MEDICAL LIBRARY

AUG 19 1948

VOL. 36 AUGUST, 1948 No. 2

AMERICAN HEART JOURNAL

For the Study of the CIRCULATION

THOMAS M. McMILLAN . . Editor-in-Chief

Associate Editors

WALLACE M. YATER
SAMUEL BELLET
LOUIS B. LAPLACE

EDITORIAL BOARD

EDGAR V. ALLEN
ALFRED BLALOCK
CLARENCE E. DE LA CHAPELLE
HARRY GOLDBLATT
TINSLEY R. HARRISON
T. DUCKETT JONES
LOUIS N. KATZ
EUGENE M. LANDIS
JOHN K. LEWIS
H. M. MARVIN
JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
HELEN B. TAUSSIG
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH
IRVING S. WRIGHT

Published Monthly Under the Editorial Direction of The American Heart Association

Published and Copyrighted 1948 by The C. V. Mosby Company, St. Louis, U. S. A.

Contents on Inside Cover

American Heart Journal

CONTENTS FOR AUGUST, 1948

Original Communications

Experience With the "Anoxemia Test" in Patients With Angina Pectoris and in Those With Atypical Chest Pain. Harold J. Stewart, M.D., Eugene L. Horger, M.D., and Charles W. Sorenson, M.D., New York, N. Y. 161

The Electrical Effects of Injury at Various Myocardial Locations. H. K. Hellerstein, M.D., and L. N. Katz, M.D., Chicago, Ill. 184

Circulatory Responses to Spinal and Caudal Anesthesia in Hypertension: Relation to the Effect of Sympathectomy. I. Effect on Arterial Pressure. Robert D. Taylor, M.D., Robert Birchall, M.D., A. C. Corcoran, M.D., and Irvine H. Page, M.D., Cleveland, Ohio 221

Circulatory Responses to Spinal and Caudal Anesthesia in Hypertension: Relation to the Effect of Sympathectomy. II. Effect on Renal Function. A. C. Corcoran, M.D., R. D. Taylor, M.D., and Irvine H. Page, M.D., Cleveland, Ohio 226

Experimental Studies on Auricular Flutter and Auricular Fibrillation. D. Scherf, M.D., New York, N. Y., F. J. Romano, M.D., Buenos Aires, Argentina, and R. Terranova, M.D., New York, N. Y. 241

Cellophane Treatment of Syphilitic Aneurysms With Report of Results in Six Cases. J. K. Poppe, M.D., Portland, Ore. 252

The Mechanism of Irregular Sinus Rhythm in Auriculoventricular Heart Block. Irving R. Roth, M.D., and Bruno Kisch, M.D., New York, N. Y. 257

Embolism at Bifurcation of Aorta. F. Stanley Morest, M.D., and Sidney Rubin, M.D., Kansas City, Mo. 277

Electrocardiographic Changes in Typhoid Fever and Their Reversibility Following Niacin Treatment. M. Rachmilewitz, M.D., and K. Braun, M.D., Jerusalem, Palestine 284

Clinical Reports

Bilateral Nontraumatic Iliofemoral Thrombophlebitis in a Child. H. L. Myers, M.D., and N. Artsis, M.D., Oceanside, N. Y. 295

Hemiplegia Following Carotid Sinus Stimulation, E. S. Brannon, M.D., Rome, Ga. 299

Abstracts and Reviews

Selected Abstracts 301

American Heart Association, Inc. 318

Vol. 36, No. 2. August, 1948, American Heart Journal is published monthly by The C. V. Mosby Company, 3207 Washington Avenue, St. Louis 3, Missouri, entered as second class matter January 23, 1917, at the Post Office at St. Louis, Missouri, under the Act of March 3, 1879. Additional entry authorized at Jefferson City, Missouri. Subscription Price: United States, its Possessions, Pan-American Countries, $12.00; In Canada and other Foreign countries, $13.00. Printed in the U. S. A.

American Heart Journal

VOL. 36 August, 1948 No. 2

Original Communications

EXPERIENCE WITH THE "ANOXEMIA TEST" IN PATIENTS WITH ANGINA PECTORIS AND IN THOSE WITH ATYPICAL CHEST PAIN

HAROLD J. STEWART, M.D., EUGENE L. HORGER, M.D., AND CHARLES W. SORENSON, M.D.
NEW YORK, N. Y.

SINCE the interpretation of pain in the precordial region is often difficult, great advance would be achieved if a means were available for separating by objective criteria those instances which are of cardiac origin, especially those which represent "angina pectoris." Physical examination, x-ray photographs of the heart, and electrocardiograms cannot be interpreted in terms of functional capacity, and the therapeutic test with nitroglycerin is not always specific.

Twenty-five per cent of White's[1] patients with a history of angina did not show any abnormality of the heart by the usual methods of examination. Biorck[2] states that in only about one-sixth of his series of one hundred fifty patients with suspected angina was the diagnosis reasonably certain. With increasing longevity, more people suffer from either organic or functional heart disease. Insurance benefits are dependent in many instances on the cardiac status of the individual. An estimate of the functional capacity of the coronary circulation would be of importance when major surgical procedures are contemplated. These are some of the reasons for a definite diagnostic implement which gives objective data about coronary sufficiency. The anoxemia test has been used in this direction.

From the Department of Medicine at the New York Hospital, and Cornell University Medica College, New York, N. Y.

Read at the 60th Annual Meeting of the Association of American Physicians at Atlantic City, N. J., May 7, 1947.

Received for publication Aug. 13, 1947.

LITERATURE

In 1921, Green and Gilbert,[3] using a rebreathing apparatus to induce a gradually progressive anoxemia, showed that lack of an adequate oxygen supply produced changes in the form of the electrocardiogram. Katz and co-workers[4] and Rothschild and Kissin[5] made similar observations. In 1938, Larsen[6] reported his experience with anoxemia in 133 subjects. His subjects breathed a mixture containing only 9 per cent oxygen for six to eight minutes. He found that there was no constant relationship between the occurrence of pain and electrocardiographic alterations. He also pointed out that the absence of an abnormal response does not rule out "stenotic lesions" of the coronary vessels. In 1933, Dietrich and Schwiegk[7] found abnormal features in the electrocardiogram which followed breathing air deficient in oxygen.

Levy and associates have made extensive observations which have resulted in establishing the method and standardizing the criteria for the anoxemia test as it is now used. They have demonstrated sufficient correlations to indicate that alterations in the form of the electrocardiogram caused by induced anoxemia can be used to estimate the functional efficiency of the coronary circulation. In 1938, Levy and associates[8] described the apparatus and method now employed in the anoxemia test, but used 12 per cent oxygen and 88 per cent nitrogen instead of the 10 per cent oxygen and 90 per cent nitrogen gas mixture now generally employed. Observations were made on thirty-seven subjects with cardiac disease and on eleven with normal hearts. During the test, the oxygen saturation in the arterial blood ranged from 67 to 83 per cent. They came to the conclusions that "there was no constant relationship between the occurrence of cardiac pain and changes in heart rate, respiratory rate, blood pressure, venous pressure, circulation time, and the degree of arterial unsaturation. Pain occurred inconstantly in repeated tests, except in two patients with aortic stenosis and in one with advanced coronary lesions."

These results prompted further studies by Levy, Bruenn, and Russell[9] who standardized the procedure as a test for coronary insufficiency. Using the same apparatus and 10 per cent oxygen and 90 per cent nitrogen, changes in the form of the electrocardiogram which followed the induction of anoxemia in 105 persons were analyzed to establish criteria for normal and abnormal responses. In 1940, Levy and associates[10] studied the actions of certain drugs (aminophylline, nitrites, digitalis) in modifying the effects of induced anoxemia in patients with coronary insufficiency. In 1941, Levy and associates[11] published the results of 326 tests carried out on 262 subjects. They obtained a positive test in 18 per cent of thirty-three patients with suspected coronary sclerosis, in 31 per cent of twenty-two patients with coronary sclerosis but no history of angina, and in 55 per cent of seventy-three patients with coronary sclerosis and a history of anginal attacks. On the basis of these studies they made the criteria for determining normal and abnormal response more rigid.

In 1942, Patterson and co-workers[12] studied 157 cases of coronary sclerosis with the anoxemia test and obtained positive electrocardiographic tests in 49 per cent and pain in another 20 per cent as presumptive evidence of coronary

insufficiency. They again pointed out, as they had earlier,[13] that the occurrence of pain during the first ten minutes of a negative electrocardiographic test is of particular importance, since in a follow-up study of fourteen such cases, four showed a positive electrocardiographic test, one suffered a coronary occlusion, and two patients died of cardiac disease. They observed at this time that their fourth criterion for a positive test, namely, "partial reversal in the direction of the T wave in Lead IVF, accompanied by an RS-T deviation of 1.0 mm. or more in this lead,"[12] occurred in normal subjects and in patients with coronary sclerosis at about equal frequency. Therefore, they discontinued the use of this criterion.

In 1941, Burnett and associates[14] used the Levy method to study 125 subjects in Colorado whose history, physical and electrocardiographic examinations, and response to exercise were normal; they were considered normal by all usual clinical standards. They found in 19.2 per cent an electrocardiographic response which, according to Levy's criteria, was indicative of coronary artery insufficiency. In their conclusion they state, "that there is some correlation between the efficiency of the coronary circulation and the electrocardiographic response seems apparent, but we have encountered 'abnormal' responses in normal subjects and 'normal' responses in abnormal subjects too frequently to justify, in our opinion, the use of this test as it is at present employed in clinical diagnosis." Patterson and associates[12] state that the differences found by Burnett and co-workers[14] were presumably due to difference in altitude, slight differences in technique, and the use of cases which were not carefully selected.

In 1943, Nylin[15] obtained 22 per cent positive tests in 163 private patients with typical or suspected angina pectoris.

In 1945, Pruitt and co-workers[16] reported a study of the anoxia test in 289 cases, using the method of Levy. They obtained seventy-one electrocardiographically positive tests in 282 of the cases with clinical evidence of angina pectoris. Of the ninety-two cases in which the history was suggestive of angina pectoris, the test was positive in 53.2 per cent. An additional 19.6 per cent experienced pain, but showed a negative test electrocardiographically. In 23.9 per cent of the cases, the test was completely negative. In 108 cases with an equivocal history, the test was electrocardiographically positive in 19.5 per cent, and in an additional 18.5 per cent of the cases, there was pain without significant changes of the electrocardiogram. In 50 per cent of the cases the test was negative.

In 1946, Biorck[2] reviewed his experience with the anoxemia test and compared it with that of Larsen (1938), Levy (1945), and Pruitt, Burchell, and Barnes (1945). He found that the test was positive in about 20 per cent of those patients "moderately suspected" of having angina. He found this figure surprisingly constant in three series of observations reported in the literature. In his own series, it was positive in 18 per cent of 100 patients without a "coronary electrocardiogram" at rest. Between 30 and 50 per cent of patients with "probable or certain coronary disease" will show a positive test. He concluded that a negative test does not exclude the existence of coronary disease.

We have been using the anoxemia test, as described by Levy and his associates, for the past five and one-half years and now add our observations to the expanding experience with this procedure.

MATERIAL AND METHOD

Our experience is based upon the results of 138 tests performed on 119 patients. The ages of the patients in all groups ranged from 20 to 77 years, the average age being 38 years. We divided our subjects into four groups.

Group I was composed of twenty-six patients who were used as controls and in whom no evidence of heart disease could be elicited. These were studied in order to gain facility with the test before using cardiac patients and also to ascertain for ourselves what the effects were in normal subjects. Their ages ranged from 20 to 57 years; there were twenty-three men and three women.

Group II included five patients, four women and one man, the youngest being 23 years and the oldest, 39 years of age: two had dextrocardia and the test was performed on them to see what effect anoxemia might have. In two patients who suffered from hypertension, the test was used to test the coronary efficiency before sympathectomy. The fifth subject was a 23-year-old Negro woman with active primary syphilis.

Group III was composed of forty patients classified as having "typical angina." There were thirty-six men and four women, the youngest being 35 and the eldest, 66 years of age. We wished to see what the results were in patients who suffered from clinically typical angina, and how close the objective correlation was in this group. The pain was typical with respect to onset, distribution, and the effect of rest, cold, emotion, and nitroglycerin; in six of these there was a previous history of coronary occlusion.

Group IV is designated as the "atypical pain" group. It was composed of forty-eight subjects who experienced vague pain in the chest or arm. In them the diagnosis of hiatus hernia, scalenus anticus syndrome, cervical rib, gall bladder disease, and neurocirculatory asthenia had to be considered. They were referred to us for clinical appraisal of the pain and with inquiry as to whether we could secure objective evidence of diminished coronary reserve. Of the forty-eight subjects, thirty-nine were men and nine were women, the youngest being 28 and the oldest, 77 years of age.

In seven subjects the test was repeated several times. Four had positive tests on all occasions, two had one positive and one negative test each, and one had a negative test on both occasions. In all of these cases, only the test with the most marked change was recorded for the analysis. The effect of the administration of aminophylline orally and intravenously was observed in two patients.

The apparatus and procedure followed were those described by Levy and associates.[11] The system consists of a tank containing 10 per cent oxygen and 90 per cent nitrogen gas which is allowed to flow at a rate approximately that of normal pulmonary ventilation. The gas mixture first flows through a humidifier, then into a rubber bag which is kept full, but not distended. The mixture

then passes through a flutter valve system, is inhaled, and a second flutter valve allows the breathed mixture to be exhaled during expiration. A two-way valve allows the observer to switch from room air to the low concentration of oxygen, or the reverse. A tank containing 100 per cent oxygen is in the circuit and can be switched on by a needle valve in case it becomes necessary to relieve the anoxemia quickly.

The test was done either in the morning before breakfast or in the afternoon, provided the patient had not had lunch beforehand. The subject on reporting to the Heart Station was made to lie down and an initial electrocardiogram taken to be used as a comparision with previous records to check on the advisability of proceeding with the test. A history was taken, especially with reference to the characteristics of the pain. Following a physical examination of the heart and lungs, the blood pressure, pulse, and respiration were taken for a baseline. During this period of rest the procedure was explained to the patient and he was told that if he should experience any pain or discomfort in the chest or arms he was to let us know by raising his hand immediately. By this time, the first record was developed and compared, and then the mouthpiece and nose clamp were applied so that the subject breathed room air and became accustomed to breathing through the apparatus. After this, several more recordings of the blood pressure, pulse, and respiration were made until basal conditions were reached. A control electrocardiogram, including the three standard leads and the precordial Lead CF_4, was then taken.

Following these preparatory studies, the test was started by turning the valve which excluded the room air and allowed a constant mixture of 10 per cent oxygen and 90 per cent nitrogen gas to be breathed. This was continued for twenty minutes if complications did not ensue; electrocardiograms were taken every five minutes. After this standard period of breathing 10 per cent oxygen and 90 per cent nitrogen gas, 100 per cent oxygen was administered for one minute and then electrocardiograms were taken at one-, five-, and ten-minute intervals with the patient breathing room air through the valve. In a number of the subjects, the 100 per cent oxygen was given only after the patients had breathed room air for ten minutes.

If pain or any unforeseen complications arose, an electrocardiogram was taken at once; 100 per cent oxygen was breathed for one minute and an electrocardiogram was then taken, followed by others five and ten minutes later with the subject breathing room air. The subject was not allowed to get up until the electrocardiogram had returned to its control form.

The amount of the RS-T deviation and voltage of the T waves was recorded in millimeters in each lead according to the recommendations of Levy and associates,[11] positive or negative direction of the deflection being indicated. When the T waves were diphasic the summation of the positive and negative deflections was recorded. Finally, the total deviation of the RS-T segments and of the voltage of the T waves for the four leads was calculated. These values for the control record were compared with those records obtained while breathing the 10 per cent oxygen and 90 per cent nitrogen mixture. The calculations

were made by one observer and checked by another. The criteria of Patterson, Clark, and Levy[12] which we used are as follows: "The test is positive when any one of the following is found:

1. The arithmetic sum of the RS-T deviations in all four leads (I, II, III, and IV F) totals 3 mm. or more.

2. There is partial or complete reversal of the direction of the T wave in Lead I, accompanied by an RS-T deviation of 1 mm. or more in this lead.

3. There is complete reversal of the direction of the T wave in Lead IV F, regardless of any associated RS-T deviation in this lead."

RESULTS

Group I (Control): In the twenty-six normal subjects, the anoxemia test was not positive electrocardiographically in anyone, and none experienced pain.

Group II (Miscellaneous): Three of the five subjects in the miscellaneous group had positive tests electrocardiographically; two of these had hypertension, and the other, active primary syphilis. The other two subjects had negative tests. Only one of this group of patients had an abnormal resting electrocardiogram.

Group III (Typical angina, Table I): Of the forty patients with typical angina, eleven had abnormal and twenty-nine had normal resting electrocardiograms. The test was positive electrocardiographically in eighteen (45 per cent). Twenty-five (63 per cent) experienced pain during the test; in fifteen (38 per cent) pain developed during the first ten minutes. Twenty-six (65 per cent) gave either a positive electrocardiographic test or developed pain in the first ten minutes of the test. Only eleven (28 per cent) had neither a positive anoxemia test nor pain.

There was no difference in the number of positive anoxemia tests (electrocardiographically) in patients with abnormal or normal electrocardiograms since positive tests were obtained in 45 per cent of each group. Eight of the eleven patients with abnormal resting electrocardiograms, however, had pain (73 per cent), while pain developed in only seventeen (59 per cent) of the patients with normal electrocardiograms.

Group IV ("Atypical pain," Table I): In the forty-eight patients, there were ten with abnormal and thirty-eight with normal resting electrocardiograms. In six subjects only (13 per cent) was the anoxemia test positive. Thirteen (27 per cent) had pain during the test and only eight (17 per cent) had pain during the first ten minutes. Thirty per cent of the subjects with abnormal resting electrocardiograms and only 8 per cent of the subjects with normal resting electrocardiograms had a positive test.

Twenty-nine subjects (60 per cent of the atypical group) had neither positive anoxemia tests nor pain, and 71 per cent had neither positive anoxemia nor pain in the first ten minutes of the test.

The results in three patients will be described.

TABLE I. COMPARISON OF THE RESULTS OF THE ANOXEMIA TEST IN PATIENTS WITH TYPICAL ANGINA AND IN THOSE WITH ATYPICAL PAIN

	TYPICAL ANGINA GROUP	"ATYPICAL PAIN" GROUP
Number of tests in same number of patients	40	48
Abnormal resting electrocardiogram	11	10
Normal resting electrocardiogram	29	38
Postive anoxemia test	18 (45%)	6 (13%)
Pain during text	25 (63%)	13 (27%)
Pain during first ten minutes	15 (38%)	8 (17%)
Positive anoxemia or pain	29 (73%)	19 (40%)
Positive anoxemia or pain in ten minutes	26 (65%)	14 (29%)
Both positive anoxemia and pain	14 (35%)	0 (0%)
Pain only	11 (28%)	13 (27%)
Abnormal electrocardiogram with positive anoxemia	5 (45%)	3 (30%)
Normal electrocardiogram with positive anoxemia	13 (45%)	3 (8%)
Abnormal electrocardiogram with pain	8 (73%)	2 (20%)
Normal electrocardiogram with pain	17 (59%)	11 (29%)
Neither positive anoxemia nor pain	11 (28%)	29 (60%)
Neither positive anoxemia nor pain in ten minutes	14 (35%)	34 (71%)

The occurrence of a positive anoxemia test in a patient with typical angina in whom the test confirmed the clinical diagnosis is illustrated by Case 1.

CASE 1.—G. K. (History No. 399691), a Greek restaurant worker, 51 years of age, gave a history of oppressive precordial pain of two years' duration. The family history revealed no evidence of cardiovascular disease. He had been a waiter and labor organizer since coming to this country at the age of 19 years. He smoked one to two packages of cigarettes a day and used alcoholic beverages only occasionally.

The first attack of precordial pain had occurred two years earlier during a labor argument. Since then he had continued to have typical anginal pain which had increased in severity and frequency. At first it was relieved by nitroglycerin, but more recently it had been uninfluenced by the drug. The attacks were typically related to exertion and emotion and, to a less extent, to overeating. The pain was pressing and squeezing in character and was localized to the precordial area. It was not possible to decide whether he had had a myocardial infarction early in the course of his present illness.

The patient was extremely emotional, excitable, and dramatic in his expressions. The ocular fundi showed moderate arteriolar thickening. The heart was not enlarged on physical examination or in the x-ray photographs of the chest (by the method of Ungerleider and Gubner).[17] The point of maximum impulse was in the sixth intercostal space, 8.0 cm. to the left of the midsternal line. There was a normal sinus mechanism and the rate was 74 per minute. The first and second heart sounds were clear and there were no murmurs. The blood pressure was 120/75.

The resting electrocardiogram was essentially normal; the anoxemia test was positive (Fig. 1).

The occurrence of a positive anoxemia test in a patient with typical angina complicated by traction diverticulum of the esophagus, in whom the test aided in differentiation of the chest pain and confirmed the clinical impression was illustrated by Case 2.

CASE 2.—B. C. (History No. 417897), a Jewish painter, 58 years of age, had had attacks of substernal pain for six years. The pain, which was squeezing in character and without radiation, was at first of great intensity and localized to the substernal region, but for the past two years it had been of less intensity. The pain had usually come on with exertion and after walking one to two blocks and could be relieved immediately by nitroglycerin. He seldom had the pain while painting, but did no climbing or strenuous lifting.

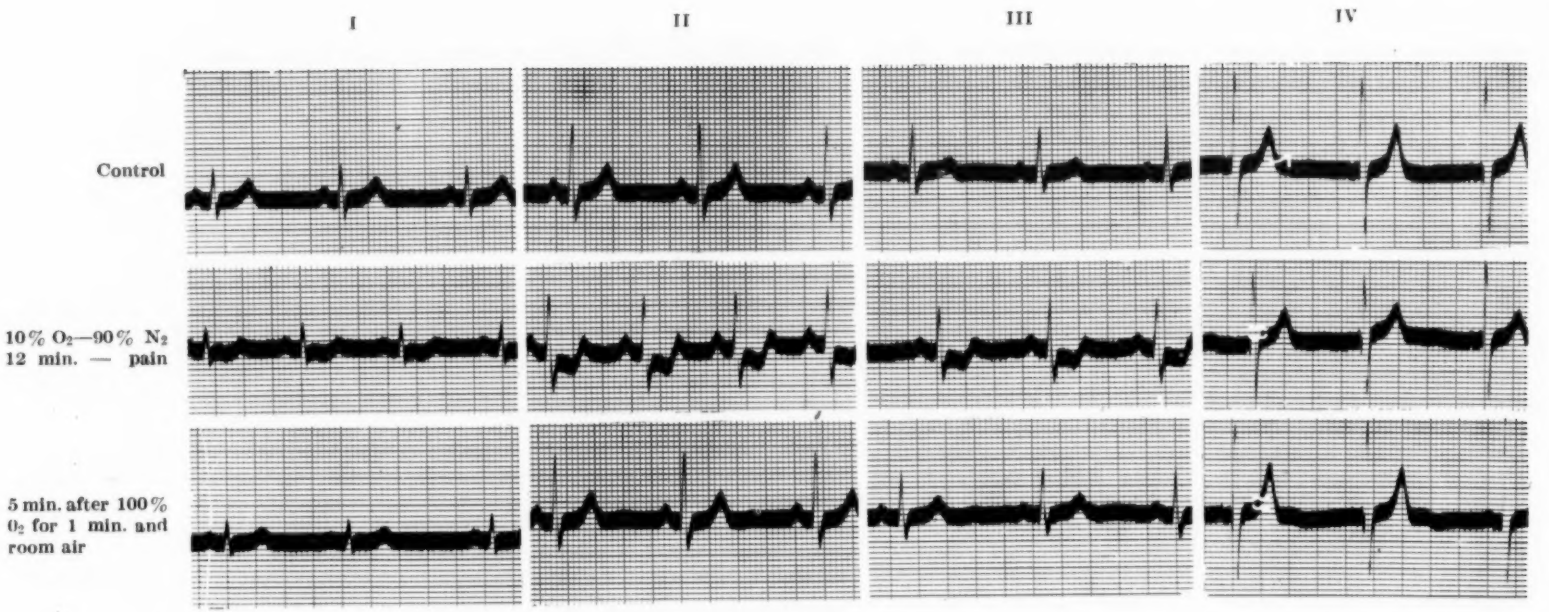

Fig. 1.—In this figure are reproduced the pertinent electrocardiograms of Case 1, G. K., in whom the anoxemia test was positive (see text). The standardization was such that 1.0 cm. deflection of the string represented 1.0 millivolt.

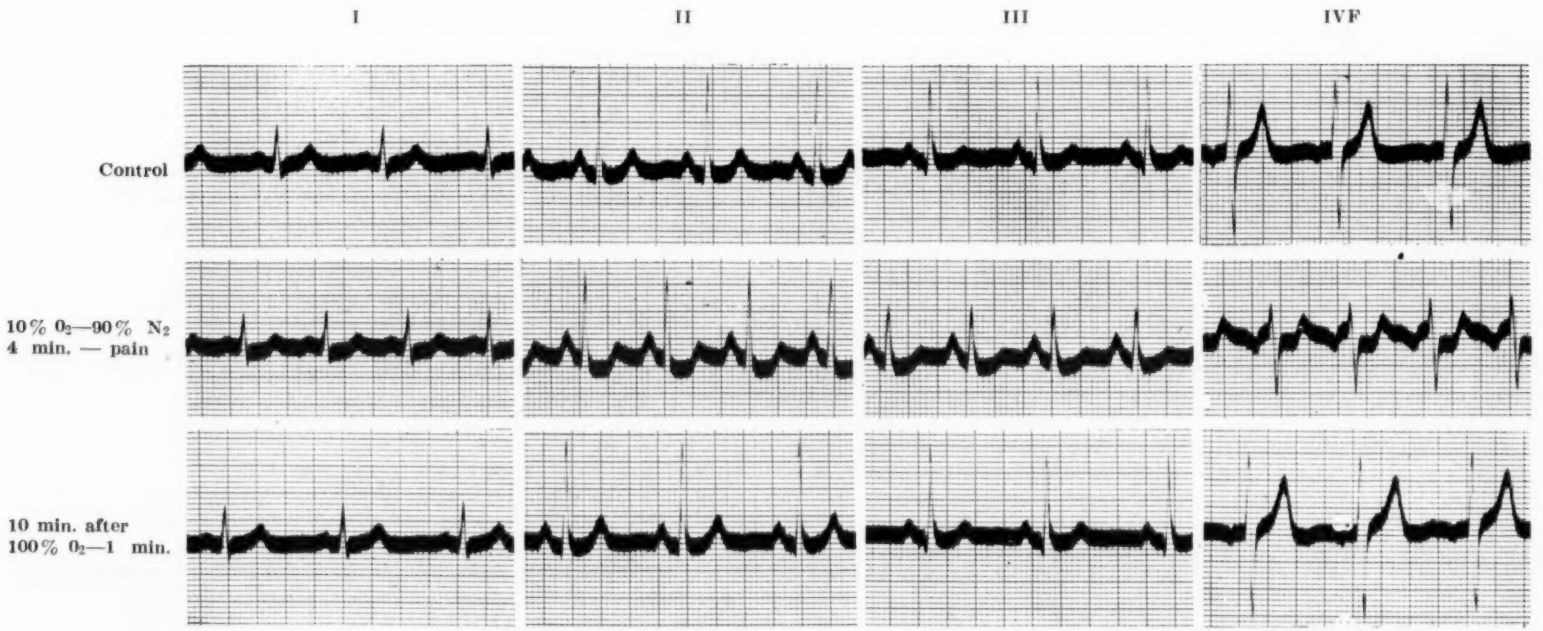

Fig. 2.—In this figure are reproduced the salient electrocardiograms of Case 2, B. C., in whom the anoxemia test was positive (see text).

He was small and thin. Funduscopic examination showed no arteriolar changes. The lungs were clear. The heart was not enlarged by physical examination or x-ray mensuration. The heart sounds were of good quality and there were no murmurs. The blood pressure was 110/70. The resting electrocardiogram was normal.

His case was of particular interest because the diagnosis of coronary sclerosis with coronary insufficiency was made when he was first seen in July, 1945, and in August, 1945, he was admitted to the Surgical Service because of regurgitation of food and a squeezing sensation in the chest after eating. X-ray study of the gastrointestinal tract revealed a traction diverticulum of the middle third of the esophagus. However, in spite of this finding, his pain was still considered typical of angina pectoris, and an anoxemia test was carried out. In four minutes pain appeared which was similar to the pain experienced on exertion, and electrocardiographic changes sufficient to indicate a positive test developed (Fig. 2).

Case 3 illustrated the occurrence of a positive anoxemia test in a subject with atypical pain in whom the test aided in establishing a diagnosis of coronary insufficiency.

CASE 3.—M. F. (History No. 425148), a 54-year-old former social worker who was referred from the Psychosomatic Clinic because of pain over the left breast of two to three years' duration. The pain had an aching quality and lasted up to five minutes at a time; it was not related to exertion, excitement, or eating. Nitroglycerin had been tried, but gave no relief. Occasionally, she had had pain in the shoulders.

She appeared to be nervous and excited. Her heart was not enlarged on physical examination or in the x-ray photographs of the chest. The heart sounds were of normal intensity. Normal sinus rhythm prevailed and there was a soft blowing systolic murmur over the apex of the heart. The blood pressure was 160/90. The resting electrocardiogram was essentially normal.

This patient was of particular interest because of various emotional problems for which she was being followed in the Psychosomatic Clinic. It was difficult to evaluate clearly her pain which was clouded by many and varied complaints. Electrocardiographic changes during the anoxemia test (Fig. 3) were of sufficient magnitude to indicate a positive response.

Effect of Hypertension on the Test.—The results of the test were compared in patients with hypertension with those having normal blood pressures in the groups with typical angina and atypical pain (Table II). Hypertension was

TABLE II. EFFECT OF HYPERTENSION ON THE ANOXEMIA TEST

	TYPICAL ANGINA		ATYPICAL PAIN	
	PATIENTS WITH HYPER-TENSION	PATIENTS WITH NORMAL BLOOD PRESSURE	PATIENTS WITH HYPER-TENSION	PATIENTS WITH NORMAL BLOOD PRESSURE
Patients in each group	11 (28%)	29 (72%)	10 (20%)	38 (80%)
Abnormal resting electrocardiogram	2 (18%)	9 (31%)	4 (40%)	6 (16%)
Normal resting electrocardiogram	9 (82%)	20 (69%)	6 (60%)	32 (84%)
Positive anoxemia test	3 (27%)	15 (52%)	3 (30%)	3 (8%)
Pain during test	7 (64%)	18 (62%)	0	13 (34%)
Pain during first 10 minutes	4 (36%)	11 (38%)	0	8 (21%)
Positive anoxemia or pain	7 (64%)	22 (76%)	3 (30%)	17 (45%)
Positive anoxemia or pain in 10 minutes	6 (55%)	20 (69%)	3 (30%)	11 (29%)
Both positive anoxemia and pain	3 (27%)	11 (38%)	0	0
Pain only	4 (36%)	7 (24%)	0	13 (34%)
Total number of patients	40		48	

Fig. 3.—In this figure are reproduced the significant electrocardiograms of Case 3, M. F., in whom the anoxemia test was positive (see text).

considered to be present if the systolic pressure was above 140 and the diastolic above 90 mm. of mercury.

In the group with typical pain there were more patients with normal blood pressure than with hypertension. The electrocardiogram was more frequently abnormal in those without hypertension than in those with it. The anoxemia test was positive twice as frequently in those with normal blood pressure as in those with hypertension (52 compared with 27 per cent). The occurrence of pain was essentially the same in both.

In the group with atypical pain, the electrocardiogram was more frequently abnormal in the hypertensive patients than in those with normal blood pressure. The anoxemia test was positive in 30 per cent of those with hypertension and in 8 per cent of those with normal blood pressure; the incidence was essentially the same in hypertensive patients with atypical pain as in hypertensive patients who had typical angina.

It appears, therefore, that in patients with typical angina the presence of hypertension does not increase the likelihood of obtaining a positive test, but makes it less likely; in atypical pain the reverse is true, namely, that hypertension increases the frequency of a positive test. In short, the presence of hypertension adds one more factor suggesting a cardiac origin of the discomfort in these patients.

Effect of Heart Size on the Anoxemia Test.—When x-ray photographs of the chest were available, the heart sizes of the subjects were estimated both by the method of Ungerleider and Gubner[17] and by the cardio-thoracic ratio; the estimation of size made on physical examination was used in those subjects not having x-ray photographs of the chest. Eleven subjects in the group with typical angina and ten in the group with atypical pain had enlarged hearts (Table III). Three patients in each group had abnormal resting electrocardiograms.

Positive anoxemia tests occurred more frequently in those without cardiac enlargement than in those with large hearts in the group with typical pain, while the reverse was the case in those with atypical pain. In short, the enlarged heart in patients with atypical pain gives one more reason to suggest a cardiac origin of the discomfort.

Effect of Both Cardiac Enlargement and Hypertension on the Anoxemia Test.—The results of the anoxemia test in patients with both hypertension and enlarged hearts in the groups with typical angina and atypical pain were also appraised (Table IV). Again, in the typical group the anoxemia test was found to be positive more frequently in those with hearts of normal size and normal blood pressure than in those with enlarged hearts and hypertension (48 compared with 29 per cent). The occurrence of pain was essentially the same in both.

In the group with atypical pain, the incidence of positive anoxemia tests in those with hypertension and enlarged hearts was much greater than in the subjects with hearts of normal size and with normal blood pressures (50 compared with 9 per cent). It is of interest that pain did not occur in any of the subjects with both cardiac enlargement and hypertension.

TABLE III. EFFECT OF CARDIAC ENLARGEMENT ON THE ANOXEMIA TEST

	TYPICAL ANGINA		ATYPICAL PAIN	
	PATIENTS WITH ENLARGED HEARTS	PATIENTS WITH HEARTS OF NORMAL SIZE	PATIENTS WITH ENLARGED HEARTS	PATIENTS WITH HEARTS OF NORMAL SIZE
Patients in each group	11	29	10	38
Abnormal resting electrocardiogram	3	8	3	7
Normal resting electrocardiogram	8	21	7	31
Positive anoxemia	4 (36%)	14 (48%)	2 (20%)	4 (11%)
Pain during test	6 (55%)	19 (66%)	3 (30%)	10 (26%)
Pain during first 10 minutes	4 (36%)	11 (38%)	1 (10%)	7 (18%)
Positive anoxemia or pain	6 (55%)	23 (79%)	5 (50%)	14 (37%)
Positive anoxemia or pain in 10 minutes	6 (55%)	20 (68%)	3 (30%)	11 (29%)
Abnormal ECG with positive anoxemia	1 (33%)	4 (50%)	1 (33%)	2 (29%)
Normal ECG with positive anoxemia	3 (38%)	10 (48%)	1 (14%)	2 (6%)
Abnormal ECG with pain	2 (66%)	6 (66%)	0	2 (29%)
Normal ECG with pain	5 (62%)	12 (57%)	3 (43%)	8 (26%)
Neither positive anoxemia nor pain	5 (45%)	6 (21%)	5 (50%)	24 (63%)
Neither positive anoxemia nor pain in 10 minutes	5 (45%)	9 (32%)	7 (70%)	27 (71%)
Total number of patients	40		48	

TABLE IV. THE EFFECT OF BOTH CARDIAC ENLARGEMENT AND HYPERTENSION ON THE ANOXEMIA TEST

	TYPICAL ANGINA		ATYPICAL PAIN	
	PATIENTS WITH BOTH	PATIENTS WITH NEITHER	PATIENTS WITH BOTH	PATIENTS WITH NEITHER
Patients in each group	7	33	4	44
Abnormal resting electrocardiogram	2	9	1	9
Normal resting electrocardiogram	5	24	3	35
Positive anoxemia	2 (29%)	16 (48%)	2 (50%)	4 (9%)
Pain during test	4 (57%)	21 (64%)	0	13 (30%)
Pain during first 10 minutes	2 (29%)	13 (39%)	0	8 (18%)
Positive anoxemia or pain	4 (57%)	25 (76%)	2 (50%)	17 (39%)
Positive anoxemia or pain in 10 minutes	4 (57%)	22 (67%)	2 (50%)	12 (27%)
Abnormal ECG with positive anoxemia	0	5 (56%)	0	3 (33%)
Normal ECG with positive anoxemia	2 (40%)	11 (46%)	2 (67%)	1 (3%)
Abnormal ECG with pain	1 (50%)	7 (78%)	0	2 (22%)
Normal ECG with pain	3 (60%)	14 (58%)	0	11 (31%)
Neither positive anoxemia nor pain	3 (43%)	8 (24%)	2 (50%)	27 (61%)
Neither positive anoxemia nor pain in 10 minutes	3 (43%)	11 (33%)	2 (50%)	32 (73%)
Total number of patients	40		48	

Results of the Anoxemia Test in Patients Who Had Sustained Previous Coronary Occlusions.—There were six patients in whom the history, examination, and electrocardiograms indicated that coronary occlusions had occurred at

some time in the past (Table V). Four (67 per cent) had a positive test or pain, while two (33 per cent) showed neither. The test was positive electrocardiographically less frequently in these subjects (33 per cent) than in the whole group of patients with typical angina (45 per cent).

TABLE V. RESULTS OF THE ANOXEMIA TEST IN PATIENTS WITH PREVIOUS CORONARY OCCLUSIONS

Patients with previous coronary occlusions	6
Positive anoxemia	2 (33%)
Negative anoxemia	4 (67%)
Pain during test	4 (67%)
Pain during first 10 minutes	2 (33%)
Positive anoxemia or pain	4 (67%)
Positive anoxemia or pain in 10 minutes	3 (50%)
Neither positive anoxemia nor pain	2 (33%)

Changes in RS-T Segments and T Waves.—None of the subjects in the control group showed total RS-T deviation of more than 3.0 mm., and in the majority the deviation was no more than 0.9 millimeter (Fig. 4). In the atypical group, however, there was a greater depression of the RS-T segments; six subjects showed an RS-T deflection greater than 3.0 millimeters. In the typical group, sixteen patients had deviations greater than 3.0 mm., while in twenty-four, deviations were less than this. This corresponds closely to the results of Patterson and co-workers.[12]

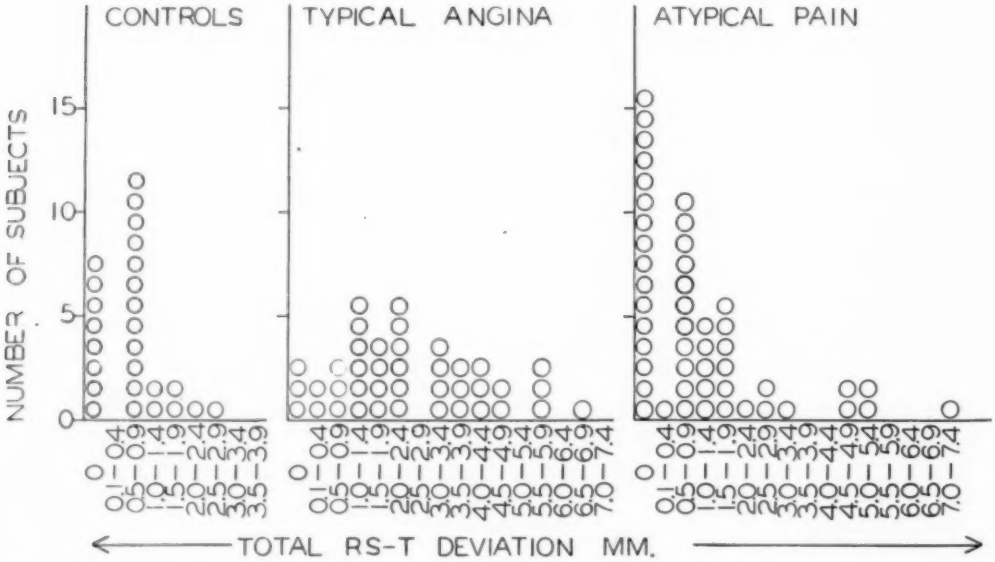

Fig. 4.—In this figure are shown scatter diagrams of the total RS-T deviations in millimeters during the anoxemia test in the control group and in the groups with typical angina and with atypical pain.

There was partial reversal of the T wave in thirteen of the subjects with typical angina. This occurred nine times in Leads I and II, eight times in Lead IV F, and only twice in Lead III among these thirteen subjects. Six subjects with atypical pain had partial reversal of the T wave: once in Lead I, three times in Lead II, and twice in both Leads III and IV F. One subject each in the control and miscellaneous group had partial reversal of the T wave; this was in Lead IV F in both cases. Complete reversal of the T wave occurred in two subjects in the miscellaneous group; twice in Lead II and once in both Leads III and IV F. Complete reversal of the T wave in Lead I occurred in one subject in the group with typical angina. In the group with atypical pain, there was complete reversal of T waves in three subjects: once in both Leads I and II and twice in Lead IV F. None of the patients in the control group had complete reversal of the T wave.

Reactions to the Test.—The most common effect of the test was the appearance of slight to marked cyanosis of the lips, ear lobes, face, or nailbeds. This occurred in over 80 per cent of the subjects. Twenty subjects had a slight headache or feeling of "fullness or pounding of the head." Seventeen subjects complained of slight dizziness. Seven subjects became nauseated and two vomited. The other reactions in order of frequency were faintness, drowsiness, tingling or numbness of fingers, fatigue, numbness of arms, choking sensation in the throat, and a heavy feeling in the chest. These symptoms occurred alone or in various combinations. Two subjects had mild hysterical reactions which prevented the test from being completed.

One patient had a vasovagal reaction during which the blood pressure fell from 260/130 to 160/90. There were no ill effects from this sharp drop in the blood pressure and the blood pressure returned to its previous level on the administration of oxygen. Another patient, a known epileptic, had a petit mal seizure which lasted approximately two minutes. His electrocardiogram during the seizure showed frequent ventricular premature contractions, but no other significant changes were found. He recovered promptly following the administration of 100 per cent oxygen. We have adhered rigidly to Levy's technique and precautions in using the test.

Correlation of the Anoxemia Test With the Exercise Tolerance Test.—Twenty-one patients had the exercise tolerance test with electrocardiograms as well as the anoxemia test. The test was carried out in the morning before breakfast or in the afternoon, if the patient had not eaten lunch. We carried out the test as follows: The patient rested lying down for one-half hour in the Heart Station. A control electrocardiogram with chest lead was then taken. The patient then walked over two steps at his own pace until he experienced discomfort, dyspnea, or fatigue. He lay down at once and a second electrocardiogram was taken. A third one was taken after an interval of twenty minutes. The control electrocardiogram was examined and compared with previous records made before the patient exercised. Whenever marked depressions of the RS-T segments or partial or complete reversal of the T waves or both resulted from exercise, the test was considered positive. There were ten subjects with typical angina,

nine with atypical pain, and two in the miscellaneous group (Table VI). In patients with typical angina, there appeared to be a close parallel between the two tests. Seventy per cent of the subjects in the typical group had a positive exercise test as evidence of coronary insufficiency compared with 45 per cent who were electrocardiographically positive in the anoxia test, or compared with 65 per cent when pain in ten minutes was included. The anoxemia test detected one positive reaction when the exercise test was negative. On the other hand, the exercise test was positive in two subjects in whom the anoxemia test was negative. One of these subjects was known to have coronary artery disease, since he had suffered coronary occlusion in the past.

TABLE VI. COMPARISON OF THE RESULTS OF EXERCISE TOLERANCE AND ANOXEMIA TESTS IN THE SAME PATIENT

	TYPICAL ANGINA	ATYPICAL PAIN	MISCELLANEOUS
Exercise tests performed	10	9	2
Positive exercise tests	7 (70%)	1 (13%)	0
Negative exercise tests	3 (30%)	8 (87%)	2 (100%)
Positive exercise tests with positive anoxemia	5	1	0
Negative exercise tests with positive anoxemia	1	0	0
Positive exercise tests with negative anoxemia	2	0	0
Negative exercise tests with negative anoxemia	2	8	2

The exercise test was positive in only one of nine patients with atypical pain, and in this subject the anoxemia test was also positive. In the other eight subjects, both the exercise and anoxemia tests were negative. Two subjects in the miscellaneous group had both negative exercise and anoxemia tests.

Effect of Aminophylline on the Anoxemia Test in Patients With Coronary Insufficiency.—The effect of aminophylline was tested in two subjects who had coronary sclerosis and positive anoxemia tests, one of whom has since died of coronary occlusion with myocardial infarction.

The first patient, J. McG. (History No. 306719), a 53-year-old white man, on Jan. 20, 1942, was found to have a positive anoxemia test with RS-T depression of 5 mm. (Fig. 5) and decrease in amplitude and inversion of the T waves in Leads I, II, III, and IVF, but no subjective symptoms of coronary insufficiency. On March 10, 1942, the anoxemia test was repeated with essentially the same results as before, the total depression of the RS-T segments being 5.5 mm.; the T waves decreased in amplitude a total of 25 mm. and became inverted in all leads.

On March 1, 1942, the subject was given aminophylline, 0.24 Gm. intravenously, and an anoxemia test performed thirty-five minutes after the injection. The RS-T segments now were only depressed 3.75 mm. and the T waves decreased in amplitude only 14.5 mm.; however, there was still partial to complete inversion of the T waves in all leads.

The patient was then placed on aminophylline, 0.2 Gm. orally, four times daily, and the anoxemia test was repeated on March 21, 1942. There were observed essentially the same changes that followed the intravenous administration of 0.24 Gm. of aminophylline, the RS-T segments being depressed 4.0 mm. and the T waves decreased in amplitude 15 mm.; yet these changes were not as marked as when the patient was receiving no medication.

He continued to take 0.2 Gm. of aminophylline four times a day orally, and on March 25, 1942, the anoxemia test was repeated, this time with the addition of 0.24 Gm. of aminophylline, intravenously, ten minutes before the test. There were occasional auricular premature contractions following the aminophylline, and the anoxemia produced a depression of the RS-T segments of only 2.5 mm. and decrease in the amplitude of the T waves of 14 millimeters.

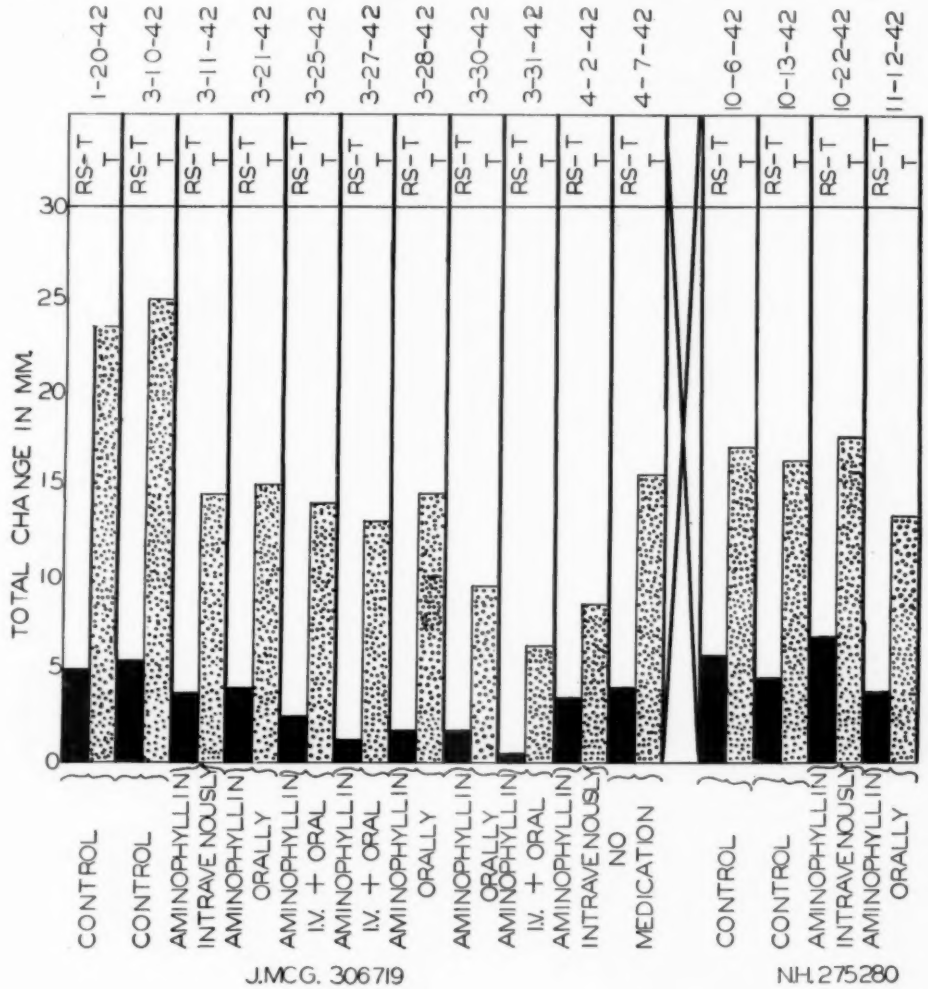

Fig. 5.—In this figure are shown the RS-T deviations and T-wave changes during the anoxemia test when patients J. McG. and N. H. were given aminophylline by mouth and intravenously (see text).

He was then placed on 0.2 Gm. of aminophylline every day. On March 27, 1942, the test was again performed, this time fifteen minutes following the intravenous injection of 0.24 Gm. of aminophylline. There was further lessening of the depression of the RS-T segments (1.25 mm.) and the T waves decreased in amplitude 13 millimeters.

On March 28, 1942, the test was again performed with the patient now on a regular oral dosage of 0.2 Gm. of aminophylline four times a day with an additional 0.4 Gm. given orally two hours prior to the test. This continued to maintain the depression of the RS-T segments at the minimum level of 1.75 mm. and the T waves decreased in amplitude 14.5 millimeters.

With the subject still on this medication, the test was performed two days later, one hour after he had received orally 0.2 Gm. of aminophylline. He continued to have an RS-T depression of only 1.75 mm., and the T waves decreased in amplitude 9.5 mm. with inversion of T_1 and T_4 only.

On March 31, 1942, with the subject on 0.2 Gm. of aminophylline four times a day, and fifteen minutes following intravenous injection of 0.24 Gm. of aminophylline the anoxia now produced a depression of the RS-T segment of 0.5 mm. and the T waves decreased in amplitude only 6.25 millimeters.

The oral administration of aminophylline was discontinued and on April 2, 1942, the test was repeated five minutes after aminophylline, 0.24 Gm., was administered intravenously. The RS-T segments now became more depressed (3.5 mm.); however, the T waves only decreased in amplitude 8.5 millimeters. The subject was given no further medication, and on April 7, 1942, the anoxemia test was again repeated. The RS-T depression of 4.0 mm. and decrease in T waves of 15.5 mm. now indicated a response approaching that observed during the control period before aminophylline was tried.

Aminophylline, in a dose of 0.24 Gm., injected intravenously, diminished the RS-T deviation 32 per cent. With the addition of 0.2 Gm. of aminophylline, administered orally four times a day, the RS-T deviation was reduced 90 per cent in the course of two weeks. The T waves were also markedly modified. These results suggest that the drug exerted a beneficial action in improving coronary circulation.

The second subject, N. H. (History No. 275880), 51 years of age, had his first anoxemia test on Oct. 6, 1942. This test showed a total depression of the RS-T segments of 5.75 mm. and changes in T waves of 17 mm. (Fig. 5). There was partial inversion of T_1 and T_4 and complete inversion of T_2. He had no subjective symptoms during the test. On Oct. 13, 1942, the anoxemia was repeated for control before aminophylline was administered. There were essentially the same changes as before, the RS-T segments being depressed 4.5 mm. and the changes in T waves being 16.25 mm., largely in the negative direction.

On Oct. 22, 1942, after a control electrocardiogram had been made, aminophylline, 0.24 Gm., was given intravenously. No significant changes were observed in records taken five and ten minutes after the injection; the anoxemia test caused no essential changes in the T waves and less marked depression of the RS-T segments as compared with the two previous tests.

After the patient had taken 0.1 Gm. of aminophylline orally four times a day for three weeks, another anoxemia test was performed on Nov. 12, 1942. There was still rather marked depression of the RS-T segments of 3.75 mm. and decrease im amplitude of the T waves in Leads I, II, III, and IVF of 13.25 mm. with partial to complete reversal of the T waves in Leads I, II, and IVF. The patient had no subjective symptoms of coronary insufficiency. These results indicate that aminophylline by mouth had a slight effect on improving the coronary circulation.

Follow-up.—As far as we have been able to learn, only one subject in the series has expired. His anoxemia test was positive. He died five years after the test was made. On post-mortem examination, a recent myocardial infarction was found. None of the subjects with negative anoxemia tests have died. Two patients with positive anoxemia tests and one with a negative anoxemia test have had posterior rhizotomy performed because of intractable anginal pain. All have done well to date, the earliest operation having been done six years ago.

Two subjects with hypertension, one with a positive anoxemia test and the other with a negative test, have had bilateral thoracolumbar sympathectomies. Two years later the lowering of blood pressure was maintained. Another subject with a negative anoxemia test and atypical pain had developed electrocardiographic changes like those seen after anterior myocardial infarction but had no clinical symptoms of coronary occlusion, and is doing well.

DISCUSSION

From these observations it is apparent that a large number of the patients who suffered from clinically typical angina pectoris exhibited significant electrocardiographic changes when exposed to low concentration of oxygen, indicating a correlation between typical angina and these objective findings; in the presence of electrocardiographic changes with anoxemia, the inference is suggested that impairment in the coronary circulation is present. On the other hand, in normal subjects during anoxia, electrocardiographic changes were insignificant. Between these two groups, namely the group of normal subjects and the group with typical angina, was a group of patients with atypical pain, in some of whom the pain may have been due to angina. In a small number of this group the electrocardiographic changes under anoxemia were significant. This experience is similar to the already published experience of other observers.[2,6,11,16] The incidence of positive tests in the group with typical angina is slightly higher than the over-all incidence in the "probable or certain coronary" cases collected by Biorck,[2] in which the range was from 39 to 50 per cent. This can probably be attributed to our selection of the cases for the typical group so that it was made up of patients about whom there could be no doubt clinically that they had angina. This selection was purposeful in order to see how close the correlation of clinical impression and the objective test was. The fact that the incidence of positive electrocardiographic tests was lower in our group with atypical pain (13 per cent) than in Biorck's[2] group of "moderately suspected cases of coronary disease" (20 per cent) was due to the placing in our group of patients referred with an inquiry concerning the nature of pain which, in many instances, was not cardiac in origin.

The use of pain induced under anoxemia as evidence of decreased coronary reserve is the cause of some concern and reflection, since one is using an induced subjective symptom which might be no more reliable than the patient's history of pain. Levy and associates,[13] however, state, "we were struck by the fact that in patients with coronary sclerosis who experienced pain during the test, even though no significant changes appeared in the electrocardiograms, the cardiac lesions were often progressive." "Of a group of fourteen subjects showing a negative reaction with pain, 28.6 per cent later had a positive reaction and 21.4 per cent had complications or died of heart disease." In a later report, Patterson and co-workers[12] state that, "the occurrence of pain, even in the absence of significant electrocardiographic changes, affords presumptive evidence of a diminished coronary reserve. Its appearance during the first ten minutes of a negative test is of particular importance." On the other hand, Pruitt and co-workers[16] state that "the occurrence of pain unattended by significant electrocardiographic changes during a test does not impress us as an event likely to contribute significantly to the solution of a diagnostic problem."

There was an appreciable difference in incidence of pain in our typical and atypical groups, 63 per cent of the former developing pain during the test as opposed to 27 per cent of the latter; 38 per cent of the typical group had pain during the first ten minutes in comparison with only 17 per cent of the atypical

group. It is apparent that if induced pain were a reliable indicator it would enhance the usefulness of the test.

The ultimate development of a positive electrocardiographic test and other evidence of heart disease in patients who originally showed only pain during the test lends weight to the argument of Levy and associates[13] concerning the importance of pain. We have not had occasion to observe this progression in our series. The occurrence of pain in the atypical group in the absence of other objective evidence of coronary insufficiency (electrocardiographic changes during anoxemia) suggests that anoxemia may lower the threshold for pain or induce types of pain other than that associated with coronary artery disease. Although pain is a subjective reaction and may be an unreliable indicator of coronary insufficiency, it seems, from the type of pain which in the majority of the typical cases appeared real and resembled the anginal pains and from the observations of Levy and his co-workers, that the development of pain during the anoxemia test should be considered, with certain limitations, as strong presumptive evidence of coronary insufficiency.

In our series, patients who had sustained previous coronary occlusions had positive electrocardiographic tests less frequently than the whole group with typical angina (33 per cent compared with 45 per cent). This indicates that patients with coronary occlusions may regain sufficient collateral circulation during the period of healing and afterward show no defect within the limits of this test as carried out. We might have expected a higher incidence of positive tests in this group if this had not been the case. This is in general agreement with the findings of Levy and associates[11] who reported two cases. One of the patients had a negative anoxemia test three years after a coronary occlusion, later died of peritonitis and pneumonia, and was found, on post-mortem examination, to have healed infarcts involving the left ventricle and interventricular septum. The other patient had a clinical picture typical of coronary occlusion and electrocardiographic changes of posterior infarction. Five months later he had a positive anoxemia test which became negative three months later still.

The results of the anoxemia tests in patients with hypertension and with enlarged hearts are of interest. In the group with typical pain, the anoxemia test was positive twice as frequently in those with normal blood pressure as in those with hypertension. On the other hand, in the group with atypical pain, the test was positive in 8 per cent of those with normal blood pressure and in 30 per cent of those with hypertension. Moreover, the test was positive more frequently in the group with typical pain in those with normal sized hearts then in those with large hearts; the reverse was the case in those patients with atypical pain. The findings were similar to those just described when the results of the anoxemia test in patients with both hypertension and enlarged hearts were compared in the group with typical angina and the group with atypical pain. It appears, therefore, in the group with atypical pain that pain in patients with hypertension or cardiac enlargement, or both, is more likely to be associated with the heart than in the group with typical angina. We have no explanation to offer for these findings.

In twenty-one patients, we were able to compare the results of the anoxemia test with those of the exercise tolerance test. The two tests are not comparable in the kind of stress to which the heart muscle is subjected by way of coronary circulation. The tests may be used to supplement each other, since either may occasionally be positive when the other is negative. In patients in the typical angina group who received both tests, the exercise tolerance test was positive more frequently than was the anoxemia test. These results are in agreement with those of Evans and Bourne.[18] The anoxemia test, however, has the following advantages over the exercise tolerance test: (1) A number of patients suffering from intermittent claudication, arthritis, or advanced age are unable to climb steps; in these, the anoxemia test only can be used. (2) We are of the opinion that the anoxemia test is safer and more easily controlled. (3) The anoxemia test can be used to study the effect of various drugs on the coronary circulation. (4) In the step test there is a lapse of time following the exercise and the taking of the electrocardiogram during which the electrocardiogram may begin reversion to its control configuration. (5) The exercise test is not without the danger of the induction of acute heart failure, while in the anoxemia test the subject is at rest and, as an added safety measure, he is attached to a closed system in which 100 per cent oxygen can be given immediately.

In one patient, the use of aminophylline decreased markedly the electrocardiographic changes induced by anoxemia. In another patient, the effect was less marked. These results are in agreement with the observations of Williams and associates.[19] These results have been interpreted as giving evidence that this drug increased the coronary circulation, presumably by coronary dilatation.

All investigators are agreed that the positive electrocardiographic test is evidence of diminished coronary reserve. Basis for this view is strengthened as evidence is collected from the analysis of the data of patients with positive tests who have later suffered coronary occlusion and from the autopsy examination of those who have died. With respect to this, one of our patients who had a positive anoxemia test died five years later and at autopsy was found to have had a myocardial infarct. Biorck[2] has collected the following data from the observation of Levy and his associates and from his own data: (1) Six patients with positive anoxemia tests and five with negative tests but anginal pain died suddenly, presumably of heart disease; (2) two subjects with positive tests had post-mortem evidence of coronary sclerosis, four with abnormal electrocardiograms and negative tests had marked coronary sclerosis, and three subjects with normal electrocardiograms and negative tests had slight coronary sclerosis or none at all. A still larger autopsy series is needed before more definite conclusions can be drawn.

The variability in response to the anoxemia test is no doubt due to several factors: (1) Although the concentration of oxygen breathed is 10 per cent, all patients do not experience the same level of anoxemia, and, therefore, the blood reaching the coronary circulation is not of uniform oxygen saturation in all patients. (2) Even if the same saturation were obtained, the caliber of the vessels in each patient would determine the flow to the heart muscle.

SUMMARY

1. It should be emphasized again that the presence of a normal electrocardiogram does not rule out angina pectoris.

2. Using the apparatus and technique described by Levy and associates, anoxemia tests were carried out on twenty-six normal subjects, forty patients suffering from typical angina pectoris, forty-six patients with "atypical pain," and six other subjects.

3. In none of the twenty-six normal subjects was a positive electrocardiographic response recorded.

4. The anoxemia test gave electrocardiographic evidence of coronary insufficiency in 45 per cent of the group with typical angina, compared with 13 per cent of the group with atypical pain.

5. When pain was included, the test gave evidence of coronary insufficiency in 73 per cent of the group with angina, and in only 40 per cent of the group with atypical pain.

6. Although only 13 per cent of the atypical cases had positive electrocardiographic changes with anoxemia, 27 per cent experienced pain, which was approximately the same as the pain in those with typical angina; this suggests the possibility that pain of an origin other than coronary disease may be aggravated by anoxemia.

7. In 32 per cent of the patients with symptomatically and therapeutically typical angina pectoris, this test failed to elicit changes under the prevailing conditions, and in 71 per cent of the group with atypical pain the results were equivocal.

8. If a patient has typical angina pectoris clinically, our experience leads us to accept the clinical impression, although the anoxemia test is negative.

9. Hypertension had no apparent effect in statistically increasing the incidence of coronary insufficiency in the group with typical pain, but in the group with atypical pain the reverse was true.

10. The presence of enlargement of the heart in patients with atypical pain increased the likelihood of a cardiac origin of the discomfort.

11. The presence of both hypertension and cardiac enlargement in the group with atypical pain increased the incidence of positive tests, which was the opposite of the results in the group with typical angina.

12. The anoxemia test when electrocardiographically positive can be used as a means of substantiating the diagnosis of coronary insufficiency, and in certain cases, is useful in the differential diagnosis of atypical pain.

13. When patients experience pain during the test but do not have an electrocardiographically positive test, the following factors should be considered in evaluating the weight to be given this manifestation: The similarity of the pain to the spontaneous pain, its prompt occurrence within a short time after beginning of the test, and the nature and reality of the pain as determined by observation of the patient during the occurrence of the pain. Under certain circumstances weight might be given to pain as presumptive evidence of coronary insufficiency. A positive electrocardiographic test, however, is more significant than a negative one, and more significant than the occurrence of pain.

We agree with Levy and his associates that weight should not be given to pain alone in instances when the payment of insurance is involved.

14. The anoxemia test can be used as a method of studying the effect of drugs on the coronary circulation.

15. In certain instances when the anoxemia test is negative, the exercise test may be positive. Great care must be used in subjecting patients to exercise to the point of inducing pain.

16. There were no serious reactions from the judicious use of the test. However, it should not be performed in every patient. Contraindications to the test are congenital heart disease, rheumatic heart disease with valvular damage, pregnancy, myxedema, epilepsy, marked emphysema or other pulmonary disease, severe anemia, and a recent coronary occlusion (within six months). If there is any evidence of congestive failure the test is definitely contraindicated.

17. Our experience with the anoxemia test has paralleled that of others.

REFERENCES

1. White, P. D.: Heart Disease, ed. 3, New York, 1944, The Macmillan Company.
2. Biorck, G.: Anoxemia and Exercise Tests in the Diagnosis of Coronary Disease, AM. HEART J. **32**:689, 1946.
3. Green, C. W., and Gilbert, N. C.: Studies on the Responses of the Circulation to Low Oxygen Tension. III. Changes in the Pacemaker and in Conduction During Extreme Oxygen Want as Shown in the Human Electrocardiogram, Arch. Int. Med. **27**:517, 1921.
4. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: The Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects. Its Bearing on the Mechanism of Attacks of Angina Pectoris, AM. HEART J. **9**:771, 1934.
5. Rothschild, M. A., and Kissin, M.: Production of the Anginal Syndrome by Induced General Anoxemia, AM. HEART J. **8**:729, 1933.
6. Larsen, K. H.: Om forandringer I elektrokardiogrammet hos sunde og syge under experimentel iltmangel, Copenhagen, 1938, Ejnar Mundsgaards Forlag.
7. Dietrich, S., and Schwiegk, H.: Angina pectoris und anoxie des herzmuskels, Ztschr. f. klin. Med. **125**:195, 1933. (Cited by Biorck[20]).
8. Levy, R. L., Barach, A. L., and Bruenn, H. G.: Effects of Induced Oxygen Want in Patients With Cardiac Pain, AM. HEART J. **15**:187, 1938.
9. Levy, R. L., Bruenn, H. G., and Russell, N. G., Jr.: The Use of the Electrocardiographic Changes Caused by Induced Anoxemia as a Test for Coronary Insufficiency, Am. J. M. Sc. **197**:241, 1939.
10. Levy, R. L., Bruenn, H. G., and Williams, N. E.: The Modifying Action of Certain Drugs (Aminophyllin, Nitrites, Digitalis) Upon the Effects of Induced Anoxemia in Patients With Coronary Insufficiency, AM. HEART J. **19**:639, 1940.
11. Levy, R. L., Williams N. E., Bruenn, H. G., and Carr, H. A.: The "Anoxemia Test" in the Diagnosis of Coronary Insufficiency, AM. HEART J. **21**:634, 1941.
12. Patterson, J. E , Clark, T. W., and Levy, R. L.: A Comparison of the Electrocardiographic Changes Observed During the "Anoxemia Test" on Normal Persons and on Patients With Coronary Sclerosis, AM. HEART J. **23**:837, 1942.
13. Levy, R. L., Patterson, J. E., Clark, T. W., and Bruenn, H. G.: The "Anoxemia Test" as an Index of the Coronary Reserve, J. A. M. A. **117**:2113, 1941.
14. Barnett, C. T., Nims, M. G., and Josephson, C. J.: The Induced Anoxemia Test (A Study by Age Groups), AM. HEART J. **23**:306, 1942.
15. Nylin, G.: Nordisk med. **18**:1045, 1943. (Cited by Biorck[20]).
16. Pruitt, R. D., Burchell, H. B., and Barnes, A. R.: The Anoxia Test in the Diagnosis of Coronary Insufficiency, J. A. M. A. **128**:839, 1945.
17. Ungerleider, H. G., and Gubner, R.: Evaluation of Heart Size Measurements, AM. HEART J. **24**:494, 1942.
18. Evans, A., and Bourne, G.: Electrocardiographic Changes After Anoxemia and Exercise in Angina of Effort, Brit. Heart J. **3**:69, 1941.
19. Williams, N. E., Carr, H. A., Bruenn, H. G., and Levy, R. L.: Further Observations on the Effects of Certain Xanthine Compounds in Cases of Coronary Insufficiency, as Indicated by the Response to Induced Anoxemia, AM. HEART J. **22**:252, 1941.
20. Biorck, G.: Hypoxaemia Tests in Coronary Disease, Brit. Heart J. **8**:17, 1946.

THE ELECTRICAL EFFECTS OF INJURY AT VARIOUS MYOCARDIAL LOCATIONS

H. K. HELLERSTEIN, M.D., AND L. N. KATZ, M.D.
CHICAGO, ILL.

THE introduction of the technique of intracardiac catheterization and the employment of intracardiac catheter electrodes[1,2] have facilitated the study of the electrical influence of the myocardium. It is thus possible to study the electrical changes within the heart cavities produced by subendocardial damage of the outer walls and septum, and by subepicardial damage of the ventricles In the present study this newer technique was used in investigating the genesis of the electrical events established by injury to the heart.

Observations were made on the effect of subendocardial, intramural, and subepicardial injury on the electrocardiogram obtained with exploring electrodes located in the cavities of the heart and on various portions of its endocardial and epicardial surfaces. Attention was focused primarily on the displacement of the S-T segment. However, attention was also given to the T-wave and QRS changes, and observations were made upon the effects of atrial injuries upon the P-T_A segment.

Two general problems were considered on the basis of the data obtained in this study:

1. *The mechanism of the development of downward displacement of the S-T segment, which is not as fully understood as that of upward displacement.* For example, the cause of downward S-T displacement noted in precordial leads in myocardial infarction, during spontaneous or induced attacks of angina pectoris, in coronary insufficiency, in digitalis medication, and in anxiety states[3] is not fully established.

2. *The significance of the effect of the subendocardial myocardium upon the electrocardiogram.* Some investigators[4,5] have held that this part of the myocardium contributes little. However, there are several recent clinical reports in which localized subendocardial infarction or myocarditis have been related to definite electrocardiographic alterations.[6-9] One case has been reported, for example, with myocardial necrosis of the anterior wall of the left ventricle, most extensive at the endocardial surface, in which downward S-T displacement appeared when a precordial exploring electrode was superjacent to the area of in-

From the Cardiovascular Department, Research Institute, Michael Reese Hospital, Chicago, Ill.
Aided by the A. D. Nast Fund for Cardiovascular Research. This department is supported in part by the Michael Reese Research Foundation.
A preliminary report was made before the American Physiological Society, May 22, 1947, in Chicago (Federation Proc. 6:128, 1947).
Received for publication Sept. 9, 1947.

jury.[6] Although the fundamental postulates of modern electrocardiographic theory, which have recently been summarized,[10] can be used to anticipate the form of the precordial electrocardiogram in cases with localized subendocardial injury, the clinical diagnosis of such involvement is not often made. Discordant views exist as to the effects of subendocardial injury. Previously, and currently, the belief has existed that extensive trauma to the subendocardium produces a downward S-T displacement at all ventricular epicardial surfaces.[3] Another group of investigators believes that such injury leads mainly to a reduction in the QRS complex with inconstant S-T segment changes, and explains this by assuming that the injury effects resulting from subendocardial damage are masked by the normal action currents arising in the uninjured superficial fibers.[11]

Accordingly, the present study was undertaken especially to obtain data upon the role of the subendocardial area of the myocardium in the production of injury currents. With such data it has been possible to re-examine the modern concepts of the genesis of the various deflections generated by injury to the heart and to relate them to the location of the injured region with respect to the exploring electrode.

METHODS

Thirty-one dogs weighing from 8 to 15 kilograms were anesthetized with intravenous pentobarbital sodium (25 mg. per kilogram of body weight). In five animals, the entire anterior chest wall was removed. In the remaining twenty-six, the chest was opened by cutting through the left fifth or sixth intercostal space, and self-retaining retractors provided wide exposure. In all animals subjected to open-chest experiments the pericardial sac was opened anteriorly from apex to base and fastened to the margins of the chest incision. This provided a stabilized cradle for the heart, and permitted ready access to all portions of its surface with the exception only of the extreme posterior basal portion of the left ventricle. These preparations remained viable for eight to twelve hours.

In all experiments unipolar direct leads were used with the indifferent electrodes placed beneath the skin of the left hind paw. The arrangement of the connection of the exploring and indifferent electrodes to the galvanometer was such that in most experiments relative positivity of the exploring electrode caused an upward deflection in the electrocardiogram. Hence, an upward S-T deviation was indicative of a relative positivity of the exploring electrode during this part of the heart cycle. In a few experiments, as indicated in the figures, the reverse connection was used.

Two types of exploring intracavity electrodes were used. The one consisted of a ureteral catheter through which a small (1.0 mm.) enamel-coated copper wire was threaded; a small German silver pellet was soldered to the end of this wire, completely occluding the tip of the catheter. The other was a nonpolarizable exploring electrode. It consisted of a 2.0 mm. glass tube, 20 cm. long, the end of which was tapered and through which extended an ordinary white darning cotton wool wick. Two square knots were tied in the cotton wool

wick which projected about 1.0 mm. from the tapered tip, effectively occluding it. The tube was filled with physiologic saline, and the untapered end was loosely packed with moist cotton. Above this was a Y tube also filled with physiologic saline. The upright limb was sealed with wax through which a nonpolarizable silver-silver chloride electrode, connected to the lead wire of the electrocardiograph, was passed. The other arm of the Y was used to fill the electrode.

The ureteral or the nonpolarizable glass tube electrode was introduced into the right heart via one of the external jugular veins, usually the right. The exact location of the tip of the electrode in the heart was determined by measurement, by direct palpation of the tip, or by gently pushing on the electrode until the tip was seen to cause a bulge in the wall of the ventricle. With the last procedure the electrode, after being located, was withdrawn 1.0 to 1.5 millimeters. The upper end of the electrode was securely fixed in the neck by a stay suture. It was found that the position of the electrode remained constant for hours.

Similar electrodes, specially bent into a rough figure 7, were introduced into the left ventricle through a small slit in the tip of the left atrial appendage. Hemostasis was maintained by a purse-string suture. The extracardiac end of the electrode was securely fixed to the left part of the chest incision by a stay suture. The tip of the electrode was free-lying and located about 1.0 to 1.5 mm. from the endocardial surface.

Control electrocardiographic records were always taken when the electrodes in the right and left ventricle were in place to exclude endocardial pressure injury, indicated by elevation of the S-T segment. This ordinarily could be eliminated, when it occurred, by altering the position of the electrode. In only two experiments was the presence of injury currents in control tracings sufficiently disturbing to require their being discarded.

The epicardial exploring electrodes were also nonpolarizable and consisted of a 2.0 cm. length of cotton wool wick soaked in physiologic saline and fastened to a Y-shaped glass tube filled with physiologic saline. One arm of the Y tube constituted a reservoir to keep the wick constantly well saturated with warm physiologic saline; a silver-silver chloride electrode was placed in the other arm and connected to the lead wire of the electrocardiograph. In some experiments the wicks were fastened to their respective spots by 7-0 atraumatic eye sutures; the experiments were usually delayed from five to twenty minutes until the mild injury produced by the ligature had subsided. In the remainder of the experiments, the injury was obviated by marking a number of spots with a cotton applicator moistened with a drop of India ink and then placing the wicks in contact with the various spots so marked.

When multiple fixed electrodes were used, records were taken from the various electrodes in quick succession by connecting each electrode on the heart surface and in the heart cavities in turn with the indifferent electrode by means of a rotary selector switch.

In some experiments observations were made of the electrical changes at the epicardial surface of the heart by using a moving wick electrode, similar in construction to the stationary wick electrode described. In these experiments,

the exploring wick electrode was moved lightly across that portion of the epicardium to be explored. This gave a continuous record of the changes in potential occurring at contiguous zones on the surface of the epicardium. Control records showed that this moving electrode itself produced no appreciable injury current. When using the moving exploring electrode, marks were made on the electrocardiographic record when the wick passed previously ink-spotted landmarks. In this way the exact location of the shifting electrode could be established from moment to moment on the finished record.

A Cambridge string galvanometer was used in six preparations; in the remainder a Sanborn Cardiette was employed. The sensitivity of the recording system was so modified that each millimeter of deflection represented 2 millivolts in the finished record, that is, 20 millivolts equalled 1 cm. of deflection. This was accomplished with the aid of a simple attenuator.*

Various methods were employed in producing injury. More than one injury was produced in the same heart in some of the animals so as to facilitate study. In such cases adequate time was allowed between experiments for complete recovery indicated by the disappearance of electrocardiographic abnormalities.

Subepicardial injury was produced in several ways (always avoiding grossly visible blood vessels):

1. By superficial suture.
2. By using a pressure electrode as described previously.[14]
3. By local application of (1 to 2 cm.) pads saturated with one-fifth molar potassium chloride solution.
4. By subepicardial injection of 0.5 c.c. of 95 per cent alcohol.
5. By heat cautery, using the red hot head of a metal screw. This gave grossly a sharply demarcated injury 0.8 cm. in diameter and 1.0 to 2.0 mm. in depth.
6. By electrocoagulation.

Subendocardial injury was also produced in several ways:

1. By pressure injury with the exploring electrode introduced into the heart cavities. The end of the electrode was manipulated so as to move it gradually toward the apex of the ventricle and cause it to press against the ventricular wall. A small bulge would be easily visible in the open-chest preparations, allowing control of the extent of injury. After a short period the pressure was gradually released by withdrawing the electrode 1.0 to 1.5 mm., so that the tip lay subjacent to the area of pressure injury. (The same electrical changes were noted when the electrode was in contact with the area of injury as when it was immediately subjacent to it.)

2. By injection of 1.0 to 2.0 c.c. of 95 per cent alcohol or of a one-fifth molar solution of potassium chloride. A long 20-gauge needle was introduced into the myocardium at an acute angle, so that the tip of the needle was at least 3.0 cm. from the point of entry. Minimal or no injury was found overlying or underlying the tip. After a control period of ten to fifteen minutes, the solution

*We are indebted to Arthur Miller, Sc.D., Chief Electrical Engineer of Sanborn Company, for suggesting this attenuator.

was injected subendocardially, the position of the infection being confirmed at autopsy. In several unsuccessful experiments, the solution extended to the epicardium and produced the typical changes of subepcairdial injury. In the successful experiments, the effects of potassium chloride were transitory and the experiment could be repeated after a suitable interval with identical results. The effects of alcohol injection persisted much longer.

3. By scrape. Scrape injury was produced by a 2.0 mm. burr. This was mounted on the end of a curved 2.0 mm. thick metal rod, and introduced into the right ventricle via one of the external jugular veins. In three animals, the burr, on the end of a rod 5.0 cm. long and 1.0 mm. in diameter, was introduced directly through a slit in the tip of the right ventricle. Surprisingly, no injury effects were noted in the intracavity leads from either chamber or from epicardial leads, even when the electrode was within 2.0 mm. of the area of entry following the introduction of the burr. After the control period, lasting up to thirty minutes, the burr was manipulated so that endocardial injury was produced by rotating the burr firmly against the overlying endocardium. By controlling the movement of the free end, and by direct visualization, specifically located scrape injury was produced on the endocarium in particular parts of the right ventricular chamber. This method was adequate and produced consistent electrical changes.

4. By curettage. Curettage of the left ventricle was produced by means of a sharp curet 2.0 by 4.0 mm. which was introduced through a slit in the tip of the left auricular appendage. After control records were taken, injury was produced in specific locations by rotating the curet against the endocardium. Only one such curettage injury was produced in each animal.

In all instances of subendocardial injury, careful necropsy examination was used to confirm the position of injury. Intravenous methylene blue was found useful in identifying the injured region at post-mortem examination. Two centimeters of a 0.5 to 1 per cent solution of an aqueous solution of methylene blue was injected before terminating the experiment. The heart was fixed in formalin solution and examined twenty-four hours later. Injured areas did not take up the dye, and thus were sharply demarcated from the surrounding bluish green uninjured regions.

Records in all cases were taken before injury, immediately after injury, and at varying intervals thereafter.

RESULTS

I. Effect of Subepicardial Injury on Direct Leads From the Epicardium.— Subepicardial injury was produced in thirty-six experiments. Tracings were made either with fixed exploring electrodes or with the moving exploring electrode.

The Electrical Changes at the Epicardium Over the Injury: The results were consistent. After injury, a diminution in the depth of the S wave occurred with a simultaneous depression of the T-R (T-Q) segment and an elevation of the S-T segment (Fig. 2,*D*, 3,*A*). In confirmation of previous work from this laboratory,[14] the shift in the level of the T-R (T-Q) segment was usually greater than that of the S-T segment. The ascending part of the R wave persisted,

forming a notch on the upstroke of the full-blown ventricular monophasic deflection, but the total height of the R wave was slightly diminished. Recovery occurred with a reversal of these changes but was accompanied or followed by the development of a deeply inverted symmetrical T wave (first three segments of Fig. 1,*D*). In two experiments the T-wave changes were found to precede the changes in QRS, S-T, and T-R. In one experiment in which a small branch of a coronary artery was tied, preliminary T-wave inversion also occurred (Fig. 1,*D* in box).

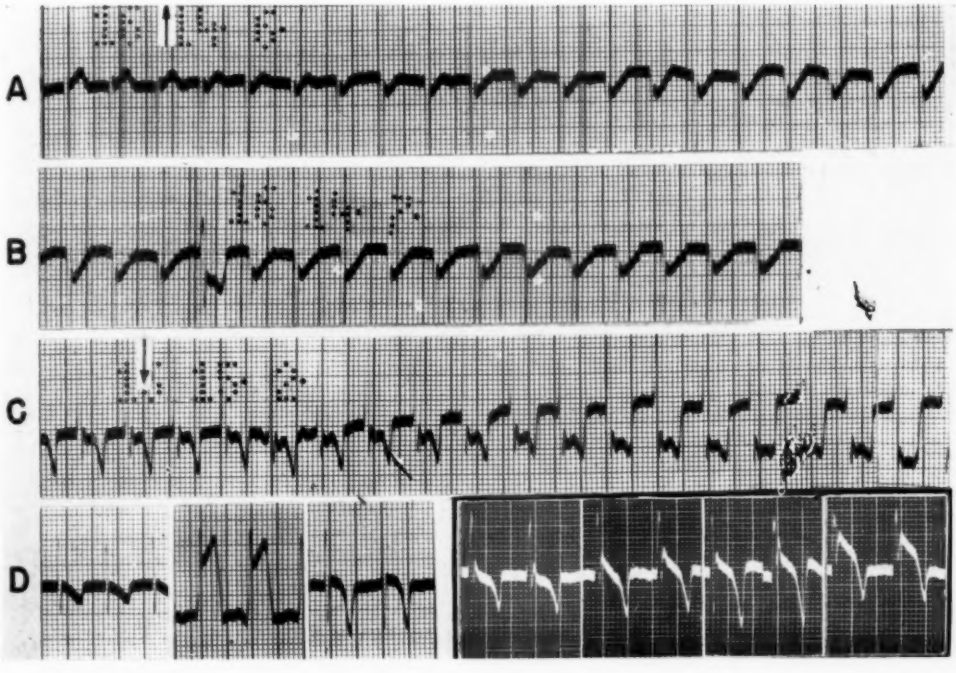

Fig. 1.—Electrical changes occurring within the left ventricular cavity and at its epicardial surface, anteriorly and posteriorly, following subepicardial injury. Rows *A* and *B* show a continuous record obtained with the exploring electrode within the left ventricular cavity. At arrow in *A*, posterior subepicardial injury of the left ventricle was produced. Fifteen minutes after *B*, the contour had returned to that before arrow in *A*. Note the progressive depression of S-T and the decreased amplitude of T which begin at once after injury is produced.

Row *C* shows a continuous record obtained with the exploring electrode on the anterior left ventricular epicardial surface. At the arrow, a posterior subepicardial injury of the left ventricle was produced. Note the progressive S-T depression and the simultaneous T-R elevation following injury.

The first three records in Row *D* were obtained in another experiment with the exploring electrode over the posterior left ventricular epicardial surface. The first record is the control; the second was taken almost immediately after injury of the subjacent subepicardial region; the third was taken fifteen minutes later. Unlike the effect on the exploring electrode within the cavity (*A* and *B*) and on the opposite epicardial surface (*C*), with this location of the exploring electrode there is a marked elevation of S-T (leading to a monophasic ventricular complex). As expected, this is replaced during recovery by a deeply inverted symmetrical T wave.

The last four records in Row *D* (enclosed in box) are from another preparation in which a small branch of the left anterior descending coronary artery was ligated, producing essentially a subepicardial infarct 1.5 cm. in diameter and 0.4 mm. in depth (confirmed at necropsy). The exploring electrode was placed on the epicardium superjacent to the injured area. The four records show, respectively, the control, a record taken immediately after the coronary ligation, and records taken ten and fifteen seconds later. The development of a deep inverted symmetrical T wave precedes the maximum S-T elevation; when the S-T deviation appears, T becomes smaller. Discussed in text.

The Electrical Changes at the Epicardium Adjacent to the Injury and at Distant Epicardial Points: Typical results are shown in Figs. 1 to 3. The results may be summarized as follows:

1. The positive S-T displacement was nowhere as great as over the area of injury.

2. Within the space of a few millimeters from the margin of injury the S-T segment quickly became isoelectric. The zone of isoelectric S-T at the margin of injury was narrow, but was always present.

3. Beyond this zone of isoelectric S-T, the S-T segment was displaced downward. The zone of downward S-T displacement extended over the same surface of the ventricles upon which the injury was located, its extent being dependent upon the size of the subepicardial injury. When the injury was large, the zone of S-T depression occupied the entire surface containing the injury.

4. As the electrode was moved around toward the epicardial surface of the opposite wall of the heart, the downward S-T displacement disappeared and a second zone of isoelectric S-T was found between the opposite walls of the ventricles. This zone of isoelectric S-T was always present regardless of the size of the subepicardial injury.

5. On the epicardial surface of the wall of the heart opposite to that injured, the S-T segment was again displaced downward. The maximum downward displacement of S-T was found in the region located perpendicular to the center of the plane of the injured area.

6. It was found that the regions beyond the periphery of the injured area later showed deeply inverted or large upright symmetrical T waves.

7. With time the T waves increased in amplitude at all points explored regardless of the occurrence of an S-T deviation following injury. At the same time S-T deviations, when they had occurred, lessened and QRS tended to return to its original appearance.

8. Continuous records taken from single points on the epicardium of the wall opposite to that injured showed that the development and regression of the downward S-T displacement was accompanied by the simultaneous development and regression of T-R (T-Q) elevation (Fig. 1,*C*). This is just the opposite of the S-T and T-R deviations found when the exploring electrode is over the subepicardial injury.

9. Lavage of the epicardium with warm isotonic saline solution accelerated the regression of the S-T and T-R displacements. With this saline wash, however, large inverted or upright symmetrical T waves developed in ten to twenty minutes, depending on the location of the exploring electrode.

The Course of Electrical Events at Equidistant Epicardial Points Outside an Area of Subepicardial Injury: In two animals, five ink spots (2.0 cm. apart) were arranged in the form of a cross on the anterior surface of the right ventricle. In four animals, nine equidistant spots (1.5 cm. apart) were arranged to form a square on the anterior surface of the right and left ventricles near the interventricular septum. In two other animals, three equidistant spots (2 cm. apart) were arranged in a straight line along the axis of the pulmonary conus. In one

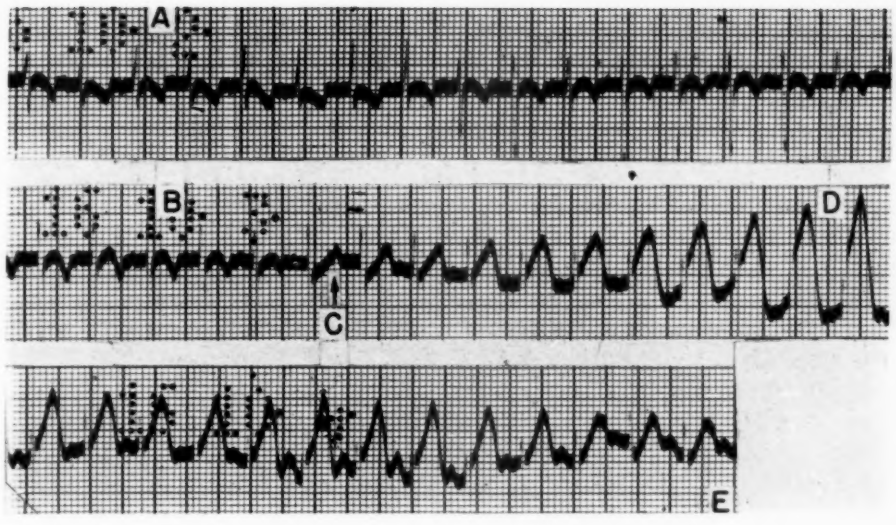

Fig. 2.—Electrical changes occurring at the epicardium in the immediate region of subepicardial injury. Three spots were marked on the epicardial surface of the right ventricular anterior wall. A pad of cotton, 3.0 mm. in diameter, was dampened with one-fifth molar potassium chloride and applied topically to the center point. A continuous record was made while the contact wick electrode was moved from the point near the base to the point near the apex. The three strips are a continuous record (between the middle and bottom strips two beats have been omitted). *A* marks the time when the electrode reached the spot 1.0 cm. basad to the injury; *C*, a spot 2.0 mm. basad; *D*, the region of injury; *E*, 1.0 cm. toward the apex. The S-T segment is isoelectric until *B*, 1.0 to 2.0 mm. from the injury; there S-T becomes depressed for two beats, then again isoelectric for two beats (*C*), and then S-T becomes progressively more elevated at the same time that the T-R segment is progressively depressed. At *D*, a large monophasic ventricular complex is present. In the bottom strip the S-T and T-R segments return quickly to the isoelectric level as the moving electrode passes beyond the injured area. (Unfortunately there is a base line movement here which obscures the shift of S-T.) Discussed in text.

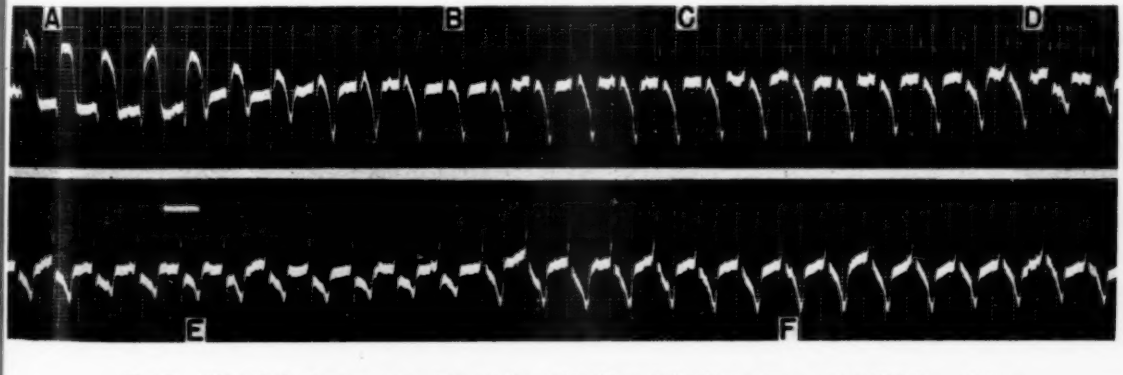

Fig. 3.—Electrical changes occurring at the epicardium following a large epicardial burn injury (2.5 cm. in diameter) located on the posterior aspect of the apex of the left ventricle. A continuous record was made, shown in the two strips, while the exploring wick electrode was moved from the center of the injured area toward the apex and then around its tip to the anterior wall and beyond the interventricular groove toward the base of the right ventricle. *A* marks the time the electrode was over the center of the injury; *B*, just beyond the periphery of the burn (which appeared normal grossly); *C*, over the tip of the apex; *D*, over the anterior apical surface of the left ventricle; *E*, over the interventricular groove; *F*, over the anterior surface of the right ventricle. Post-mortem examination revealed the burn injury to be mainly subepicardial with hemorrhagic strands extending to the subendocardium. Over the injured area (*A*) there is a small Q wave, marked S-T elevation, and less T-R depression, giving rise to a monophasic curve. As the electrode reached the edge of injury (*B*), the S-T and T-R deviations disappeared and a progressively increasing inverted T wave appeared. The S-T segment at the tip of the apex (*C*) is isoelectric, but over the anteroapical part of the left ventricle (*D*) it becomes depressed; this depression increases over the interventricular groove (*E*) and then lessens and disappears over the anterior wall of the right ventricle (*F*). An intracavity exploring electrode in the tip of the left ventricle near the burned area showed S-T elevation which is attributed to the incomplete transmural injury found at necropsy. Discussed in text.

animal, three such equidistant spots were marked on the anteroapical wall of the left ventricle.

After control records were taken, localized subepicardial injury was produced in each preparation at the center spot. In two animals, alcohol was used. The injury usually measured 0.5 to 0.8 cm. in diameter and was from 1.0 to 2.0 mm. in depth. The remaining spots, therefore, were well outside the margins of the injured area. In four animals a superficial suture was used which produced an injured area of 1.0 to 2.0 millimeters. In the remaining three animals a cautery was used to create an injured area 0.8 cm. in diameter and 1.0 to 2.0 mm. in depth. Records were taken immediately after the production of injury and repeated at lengthening intervals until the records showed a return to the normal contour, a period varying from one to two hours. The findings in all but one experiment were similar and a typical one is shown in Fig. 4.

The results of this group of experiments on subepicardial injury confirm and amplify the findings previously reported from this laboratory,[14] and can be summarized as follows:

1. Changes in the contour of the QRS complex described in the preceding section, indicating an alteration in the pattern of impulse spread, occurred first in the injured area and later also in other areas outside the injured region.

2. An elevation of the S-T segment occurred which was maximum over the injured region and became smaller in regions removed from the injury. These S-T changes tended to disappear with time. The S-T displacement occurred sooner and to a greater extent at points nearer the base than at points nearer the apex of the heart. One experiment which was an exception, the three equidistant points being on the anteroapical wall of the left ventricle and the injury being produced by suture, showed a greater injury effect in the apically than in the basally located point. This exception may be explained by an inadvertent ligation of a small blood vessel supplying the apical portion of the heart. As would be expected, in the experiments with eight distant exploring electrodes, the magnitude of the injury effects varied with the distance from the site of injury.

3. A deeply inverted symmetrical T wave appeared some time after injury was produced, both in the region of injury and in the surrounding regions. These deeply inverted T waves developed in the areas surrounding the injury regardless of whether or not S-T displacement had occurred. These T waves tended to disappear with time.

These injury changes which appear after a lag in the zone surrounding injury may be related to the spread, by diffusion or by lymphatics, of the products of injury. It must be emphasized that all the points were located on the wall injured.

Only in two experiments did the points not all lie in the same plane. In these experiments cautery injury was produced in the middle of five equidistant points arranged in a straight line along the pulmonary conus. Four of the points lay on the anterior surface of the heart; the fifth, near the lateral margin of the right ventricle, lay on its lateral wall. Elevation of the S-T segment occurred at the point of injury and at the points on the anterior wall. However, the

point on the right lateral border showed S-T depression, as had been found in experiments described in the preceding section in which the electrode was placed on the wall of the heart opposite to that injured.

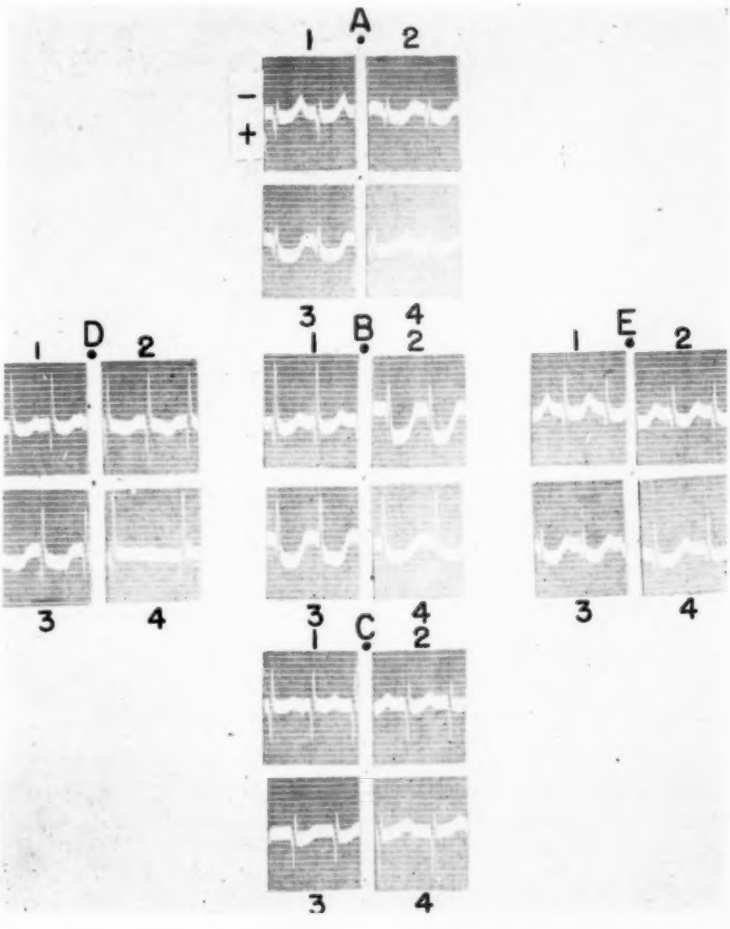

Fig. 4.—Spread of subepicardial injury effects. Note that the polarity used in this experiment was the reverse of that shown in Figs. 1 to 3 so that an S-T depression here is equivalent to an S-T elevation in the preceding figures. Relative negativity of the exploring electrode in this experiment gave an upward deflection instead of a downward one as in the previous figures.

The five groups of records show the control (*1*), and records taken, respectively, immediately, five minutes, and forty-five minutes after injury (*2*, *3*, and 4). Subepicardial injury, 8.0 mm. in diameter, was produced at Site *B* in the center of the anterior surface of the right ventricle by heat cautery. The other four sites were each 2.0 cm. distant from this center spot and 90° from each other. They were all equidistant from the edge of injury. No gross blood vessels were visible at the site of injury. Site *A* was near the A-V sulcus; *C*, near the apex of the right ventricle; *D*, near the lateral border of the right heart; *E*, near the pulmonary conus. It will be noted that, as expected, the S-T displacement is greatest over the injury (*B*) and is unequal in the four other equidistant spots (*A*, *C*, *D*, and *E*). Thus, for example, the S-T depression is least in *C* and greatest in *A*. Furthermore, the evolution of the S-T deviation in time was not uniform. In the four distant sites the S-T deviation is maximum at five minutes (Segments *3* in *A*, *C*, *D*, and *E*) while over the injury it is maximum immediately after injury was induced (Segment *2* in *B*). Furthermore, at Site *E*, the S-T deviation persisted for forty-five minutes while at the other distant sites (*A*, *C*, and *D*) it had practically or entirely disappeared by this time. The spread of injury is thus unequal and its evolution in equidistant spots nonuniform. Discussed in ext.

II. Effect of Subepicardial Injury on Intraventricular Leads.—Twenty-two different experiments were performed in ten animals, injury being produced by cautery or topical one-fifth molar potassium chloride. In five animals, records were obtained from both right and left cavities; in the remaining five, records were obtained only from the right ventricular cavity. Before a second experiment was performed in the same animal, sufficient time was allowed for complete recovery from the injury effects of the previous experiment.

In all but one of these experiments the changes in the tracings were of the same type. A typical result is shown in Fig. 1,*A* and *B*. The changes consisted of an immediate depression of the S-T segment, with the T-R (T-Q) segment remaining practically isoelectric, the T wave upright, and the QS becoming slightly smaller. With recovery, the S-T segment returned to its isoelectric level and the QS returned to its previous size or became slightly larger than in the control electrocardiogram. At the same time the T wave became more inverted and developed a symmetrical configuration. These T waves sometimes appeared before the S-T had returned to its isoelectric level.

In one experiment, in which an area of injury was produced on the anterior surface of the right ventricle by cautery, a tall upright T wave appeared in records from the right ventricular cavity, without any S-T elevation and only 0.5 mm. decrease in the depth of QS. This was the immediate effect. Three minutes later the S-T segment became elevated, and the T wave became even taller. Complete recovery occurred in fifty-five minutes. Autopsy examination revealed a subepicardial area of coagulation 2.0 cm. in diameter and 2.0 mm. deep. However, in the subjacent subendocardial myocardium, there were multiple minute areas of hemorrhage. It is not unreasonable to assume, therefore, that this unusual change in the intracavity lead was due to the subendocardial damage secondary to the transmitted heat. This is illustrated diagrammatically in Fig. 17 (lower left hand drawing).

In two experiments, subepicardial burn injury was produced on the lateral wall of the left atrium and its appendage. A tracing taken from the middle of the left atrial cavity showed depression of the P-Q ($P\text{-}T_A$) segment. The changes in the atrial cavity following subepicardial atrial damage, therefore, are analogous to the S-T depression in the ventricles following ventricular subepicardial injury. The $P\text{-}T_A$ segment is the atrial analogue of the S-T segment of the ventricles. Thus, injury of the atria operates similarly to injury of the ventricles.

III. Effect of Subendocardial Injury of the Outer Walls of the Ventricles on Endocardial and Intracavity Leads.—Subendocardial injury was produced by pressure electrodes introduced into the heart cavities forty-five times in eleven animals with the same results. A typical experiment is shown in Fig. 5. The following reversible changes were noted:

1. A decrease in the amplitude of the QS, so that it formed a notch on the upstroke of the full-blown monophasic ventricular deflection (Fig. 16, Chart 5).
2. A depression of the T-R (T-Q) segment.
3. An elevation of the S-T segment.

4. The extent of the S-T and T-R displacements was not equal. However, the pattern of development and disappearance of T-R was similar to that of S-T (Fig. 16, Charts 3 to 6). In some experiments the T-R depression was great while the S-T elevation was less than 1.0 millimeter. Occasionally, the opposite occurred. Sometimes the amount of displacement of S-T and T-R was equal. However, in the majority of experiments, the shift of the T-R was greater than that of the S-T segment.

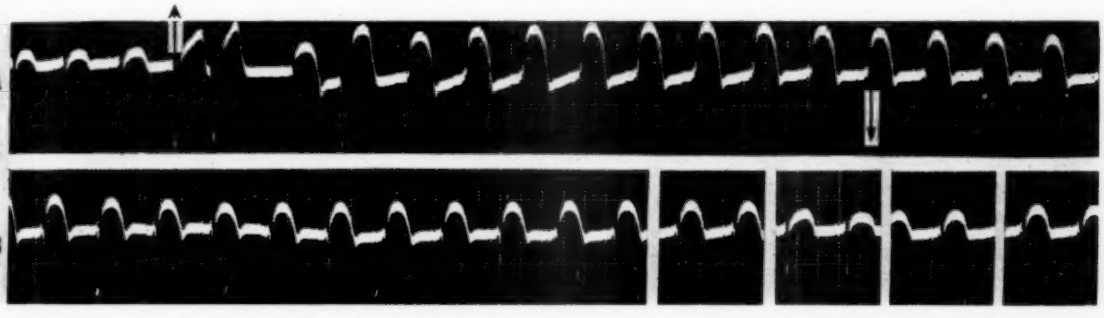

Fig. 5.—Electrical changes occurring at the endocardium of a subendocardial injured area. Subendocardial injury of the right ventricle was produced by endocardial pressure with an exploring electrode. Strip *A* and the first part of Strip *B* are a continuous record. The period of electrode pressure is shown by the two arrows in Strip *A*. The last four segments of Strip *B* were taken twelve seconds, twenty-four seconds, one minute, and fifteen minutes after release of pressure, respectively. With pressure, two successive ventricular premature systoles appear and are followed, after a normal beat, by a third premature systole. Note the development of S-T elevation and the lesser degree of T-R depression following injury and beginning regression even while pressure was maintained. Injury also led to the transient disappearance of the S wave. Restoration of the original contour is progressive and is almost complete within one minute after release of the pressure. These results parallel those previously observed with a similar electrode applied epicardially.[14] Discussed in text.

5. The persistence of the residual injury effects increased with more severe injury. Thus, after pressure for five seconds, complete restoration occurred in one beat; after pressure for four minutes complete restitution required twenty-two minutes. Occasionally, slight S-T elevation remained as a residue. Necropsy revealed areas of subendocardial hemorrhage measuring about 0.3 to 0.8 cm. in diameter, when endocardial pressure injury was produced repeatedly in the same site.

6. At the onset of the subendocardial pressure injury, several premature beats with widened QRS complexes occurred, followed by typical T-R, S-T, and QS changes (Fig. 5,*A*). These premature beats probably originated locally at the margin of injury.[15] In several instances, normally spaced beats with widened QRS complexes occurred with injury and disappeared when the pressure was released. These probably represent local focal intraventricular block (Fig. 6,*A*, *B*, and *C*).

7. In only two experiments, with mild pressure, did deeply inverted T waves occur without deviation of the S-T segment. However, when the pressure was increased the usual T-R and S-T changes developed. In another experiment, the S-T changes were slight while the T wave became significantly deeper after prolonged pressure injury. In still another experiment, the T wave became

deeper before the monophasic ventricular injury curve appeared. In a fifth experiment, the T wave became deeper during recovery from the injury effects.

Similar changes were obtained with other methods of subendocardial injury (Fig. 7, Row 3, and Fig. 17, left middle chart).

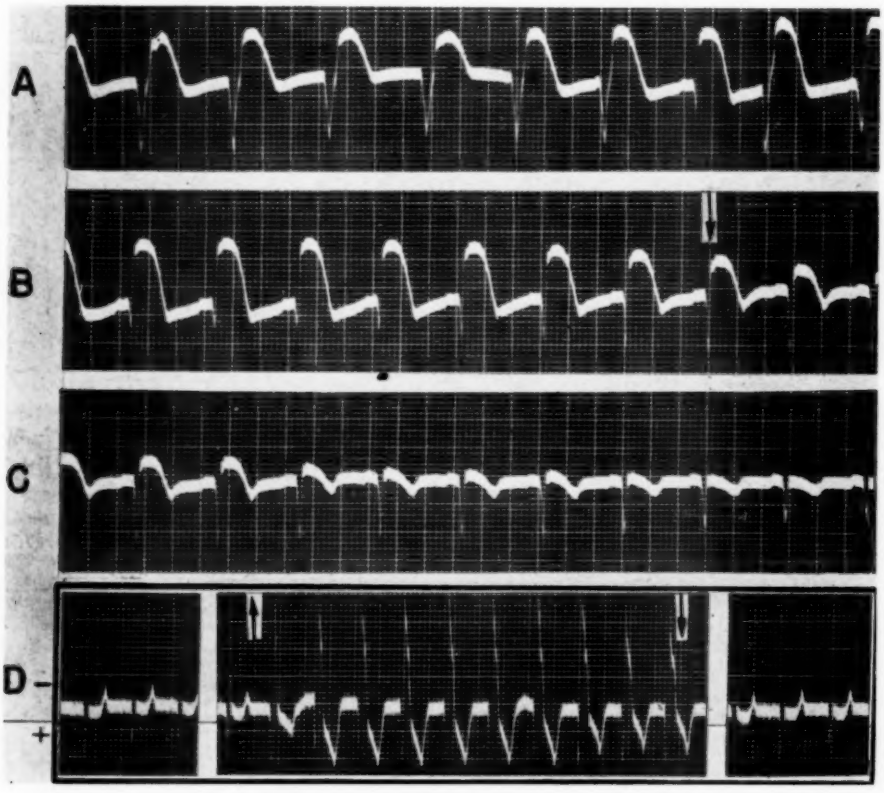

Fig. 6.—Production of local focal intraventricular block by endocardial pressure injury in the right ventricle. Rows *A*, *B*, and *C* represent a continuous strip of the first experiment. In this dog with closed chest, subendocardial injury was produced by the same kind of pressure electrode as that used in Fig. 5. Injury was produced before Record *A* was taken and the pressure gradually lessened. Arrow in *B* shows end of pressure. The last beats in *C* can serve as a control since this was the contour found before pressure was applied. Note that, unlike endocardial leads in animals with open chests, in which T is upright, the T wave is inverted in this animal with closed chest. With maximal pressure, in *A*, the QS widens, returning to its normal duration upon release of pressure. In Strip *B*, QS, after pressure release, becomes smaller, returning to its control depth as recovery continued (*B* and *C*). Injury in this case, as in Fig. 5, caused S-T elevation and a lesser degree of T-R depression which progressively lessened during recovery. A sinus arrhythmia is present. The preliminary QRS widening is attributed to a prolongation of depolarization in the injured area; a local focal intraventricular block.

In the second animal, with chest open, (Row *D*) endocardial injury was applied by pressure and the exploring electrode was placed on the superjacent epicardium. The first segment is the control. The middle segment shows, between arrows, the production of subendocardial injury. The last segment shows the recovery; two beats are omitted between the middle and last segments. In this instance, the entire alteration of pressure injury is dominated by the local focal intraventricular block; QRS is broadened and the ST-T is deviated in a direction opposite to QRS. It is apparent that local focal intraventricular block produced in the subendocardium may be recorded from the superjacent epicardial area. In this experiment, as in Fig. 4, the polarity of the electrodes was reversed. Discussed in text.

In two experiments, subendocardial injury was produced in the right atrium with a pressure electrode. This caused a positive deviation of the P-Q ($P\text{-}T_A$) segment, with its return to control levels upon relief of pressure (Fig. 15). This again is analogous to the S-T changes obtained with similar pressure on the endocardium of the ventricles.

IV. Effect of Subendocardial Injury on Direct Epicardial Leads.—Subendocardial injury was produced by pressure electrodes introduced into the heart cavities in eleven animals, by the subendocardial injection of 95 per cent alcohol in four animals and of one-fifth molar potassium chloride in four animals, by curet in three animals, and by scrape in six animals. These injuries were confined to the outer walls of the ventricles, exclusive of the interventricular septum.

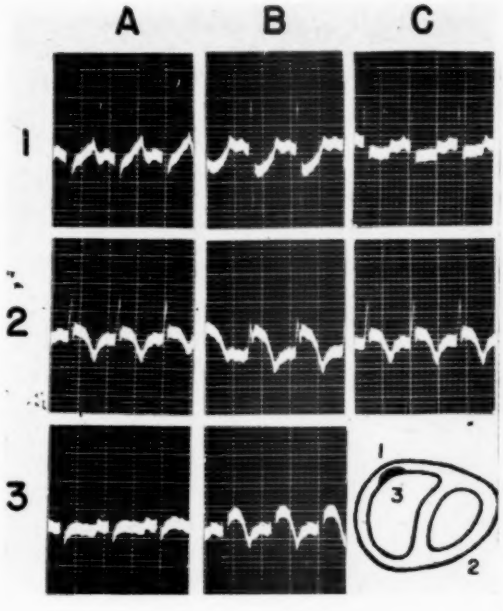

Fig. 7.—Electrical changes occurring at the epicardium superjacent to a subendocardial injury, at the posterior epicardium of the left ventricular apex, and in the right ventricular cavity following injury (by scrape) of the subendocardium of the anterior right ventricular wall. The diagram in the lower right-hand corner shows the location of injury and the position of the three exploring electrodes. The numbers correspond to the rows showing the records obtained with the exploring electrode in the three locations. Column *A* shows the control; *B* and *C* are records taken, respectively, immediately and nine minutes after the injury was induced. Following injury (Column *B*), an S-T depression develops when the electrode is on the epicardium over the subendocardial injury (Row *1*), and an S-T elevation appears when the electrode is in the right ventricular cavity (Row *3*) and posterior epicardial surface of the left ventricle (Row *2*). At the same time R becomes smaller in Position 1, and S disappears in Position 2. Discussed in text.

Electrical Changes Produced at the Epicardial Area Over the Subendocardial Injury: Consistently, a depression of the S-T segment and minimal diminution in the amplitude of the R and S wave followed injury (Figs. 7, Row 1, 10, Row 1, 11, Row 2, and 12,*B*). In one experiment, a tall upright symmetrical T wave appeared. (Only when the injury extended to involve the subepicardium were

these typical changes absent and the findings of subepicardial injury noted instead.)

Occasional premature beats with wide QRS complexes were seen in tracings made while the injury was being produced. In two animals, subendocardial pressure injury produced by the pressure electrode resulted in the appearance of widened QRS complexes occurring at the same rate as in the control records (Fig. 6,*D*). These beats are similar in character to those described in the preceding section and probably, like them, signify local focal intraventricular block.

Electrical Changes Produced at Epicardial Areas Distant From the Subendocardial Injury: In these experiments data were obtained by recording either with fixed or moving exploring electrodes. Typical results are shown in Figs. 7, Row 2, 10, Rows 2 and 3, 11, Row 1, and 12.

As the electrode was moved away from the epicardial region overlying the subendocardial injury, the S-T depression became less marked and eventually disappeared. As the electrode was moved to the epicardial surface of the opposite wall, S-T became elevated and its elevation increased until a zone was reached 180 degrees from the point of subendocardial injury. Thus, subendocardial injury of the anterior wall of the right ventricle caused an upward S-T deviation in epicardial leads from the posterior wall of both the right and left ventricles. Subendocardial injury of the posterior wall of the left ventricle caused S-T elevation in leads from anywhere on the anterior wall of the ventricles and the S-T segment was isoelectric in leads from the lateral wall of the ventricles. The magnitude of the zones of downward and upward S-T displacement was roughly proportional to the area of injury. In the majority of experiments the magnitude of the depression of S-T over the region of injury was greater than its elevation at distant points. However, in several experiments the S-T displacement at a distance was equal and opposite to the S-T displacement over the injury In one remarkable experiment where a very extensive subendocardial injury was produced in the anterolateral wall of the right ventricle, marked S-T elevation took place at the lateral margin of the left ventricle with only slight, though definite S-T depression over the area of injury (Fig. 11).

V. Effect of Subendocardial Injury of One Side of the Interventricular Septum on Epicardial and Intracavity Leads.—Localized scrape injury was produced on the right side of the interventricular septum in three animals and on the left in two. The injured areas measured from 1.5 to 2.5 cm. in diameter, and consisted of roughened endocardium with hemorrhage into the subendocardial myocardium extending for a depth of from 1.0 to 3.0 millimeters. Ventricular fibrillation was easily produced by injurying the basal part of the interventricular septum, expecially on the right side. Single or serial electrical shock[16,17] was successful in breaking such ventricular fibrillation without producing detectable epicardial damage. In one animal, ventricular fibrillation occurred when the probe was introduced into the heart via the jugular vein. A single electric shock broke the fibrillation. Subsequent control records revealed no injury effects on the epicardial surfaces or within the cavities.

Typical results are shown in Figs. 8 and 9 and diagrammatically in Fig. 17 (last two drawings of middle row). In all experiments the expected effects occurred in ipsilateral intracavity leads. These were the same as when

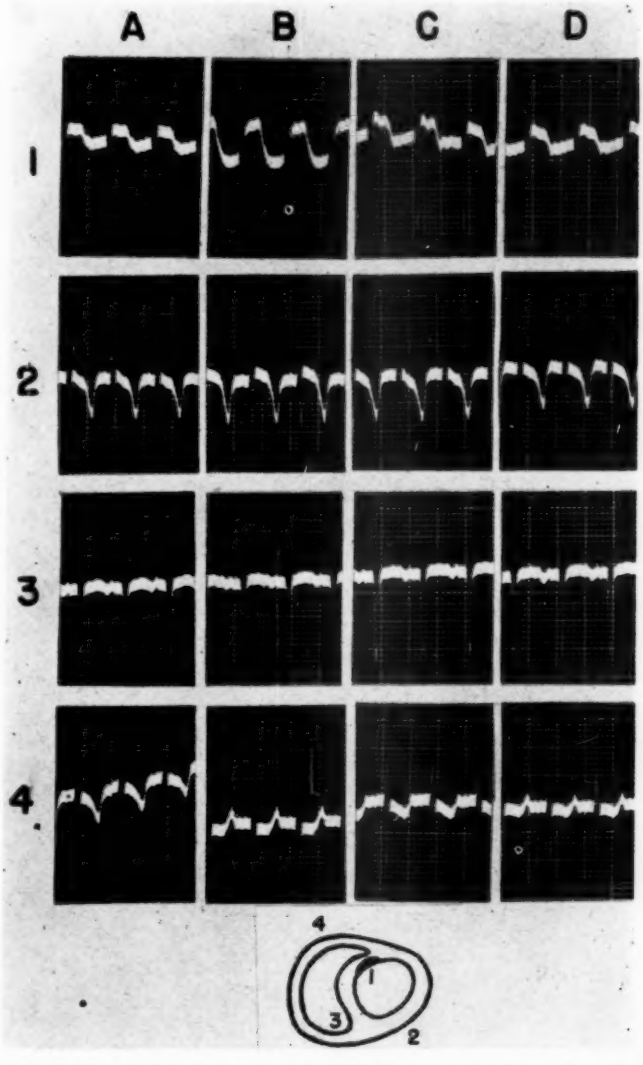

Fig. 8.—Effect of injury (by scrape) of subendocardium of anterior basad part of left side of interventricular septum. Arrangement of figure as in Fig. 7. Diagram shows location of injury and position of four exploring electrodes employed: *1* is in left ventricular cavity; *2*, on the epicardial surface of anterolateral wall of the left ventricle; *3*, in right ventricular cavity near its apex; *4*, or the epicardial surface of anterior wall of right ventricle. Rows *1* to *4* show, respectively, the records obtained with the exploring electrodes in these four sites. Column *A* represents the control; *B*, *C*, and *D* were taken, respectively, immediately, five, and ten minutes after the septal injury was produced. Following injury there is a definite S-T elevation in a lead from the left ventricular cavity (Row *1*) and a slight elevation of S-T when the electrode was over the epicardium of the left ventricle (Row *2*); at the same time there is S-T depression with the electrode over the epicardium of the right ventricle (Row *4*). No S-T deviation occurred in a lead from the apical part of the right ventricular cavity (Row *3*). These results, like those of the preceding experiments, are expected on the basis of the spatial relationships of the electrodes to the injury. Discussed in text.

subendocardial injury was produced in the outer walls of this ventricle. An upward S-T displacement occurred. At the same time there was a downward S-T displacement in the contralateral intracavity lead. In one experiment, however, no change was noted in the contralateral intracavity lead. In this animal

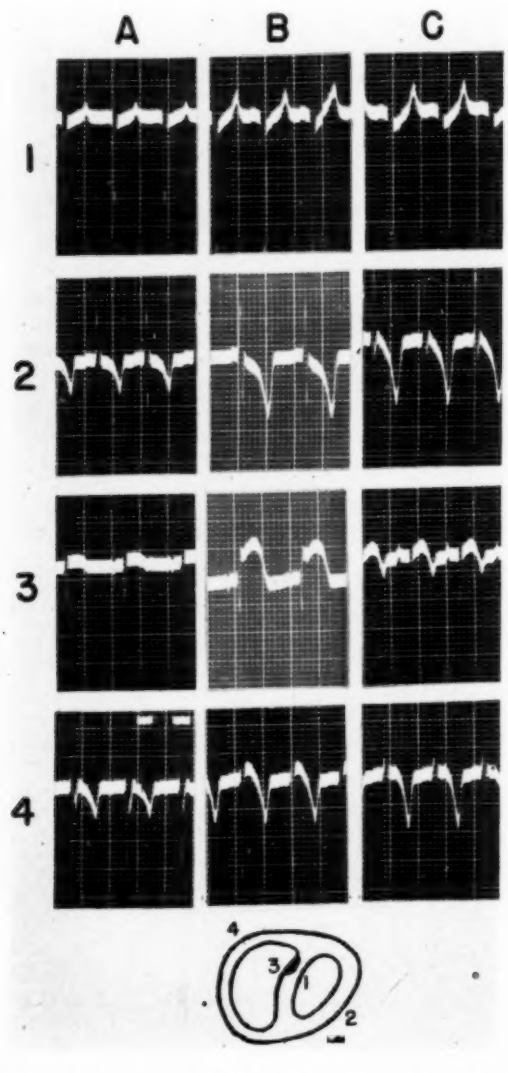

Fig. 9.—Effect of injury (by scrape) of the subendocardium of the right side of interventricular septum. Arrangement of figure as in Fig. 7. Diagram shows location of injury and position of four exploring electrodes employed: *1* is in left ventricular cavity; *2*, on the epicardial surface of anterolateral wall of left ventricle; *3*, in right ventricular cavity; *4*, on the epicardial surface of anterior wall of right ventricle. Rows *1* to *4* show, respectively, the records obtained with the exploring electrodes in these four sites. Column *A* represents the control; *B* and *C* were taken, respectively, immediately and ten minutes after the septal injury was produced. Following injury there is a definite S-T elevation in a lead from the right ventricular cavity (Row *3*) and to a lesser extent in a lead from the epicardium of the right ventricle (Row *4*); at the same time there is S-T depression in a lead from the left ventricular cavity (Row *1*) and over the epicardium of the left ventricle (Row *2*). Discussed in text.

the injury was produced in the upper part of the left side of the interventricular septum (Fig. 8). At autopsy it was found that the septum bulged into the right ventricle, and that the intracavity electrode was located in the tip of the right ventricle, so oriented that it was distant from the injury and lying in the plane parallel to the major edge of the injury. Thus, with the exception noted, injury of the subendocardium of the interventricular septum caused opposite changes in the S-T segment in the two ventricular cavities.

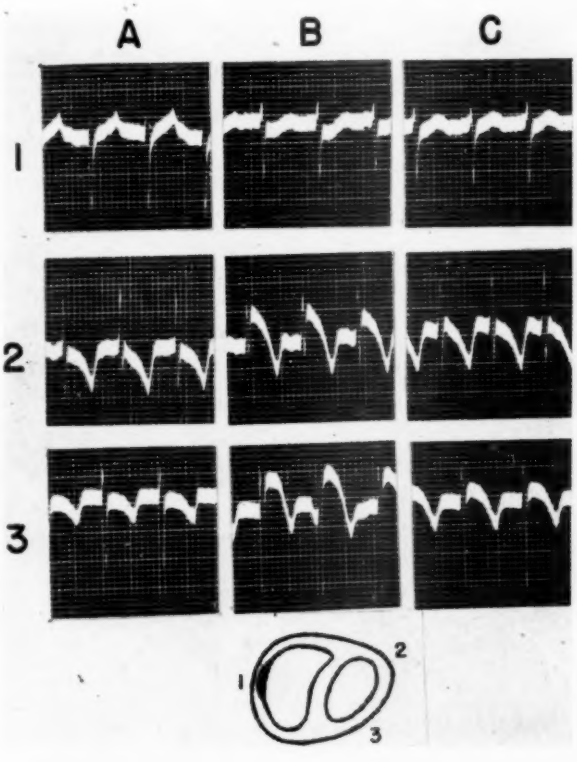

Fig. 10.—Effect of injury (by scrape) of the subendocardium of the anterolateral wall of the right ventricle. Arrangement of figure as in Fig. 7. Diagram shows location of injury and position of three exploring electrodes employed: *1* is on the epicardial surface superjacent to the endocardial injury; *2*, on the epicardial surface of the anterolateral apical wall of the left ventricle; *3*, on the epicardial surface of the posteroapical wall of the left ventricle. Rows *1* to *3* show, respectively, the records obtained with the exploring electrodes in these three sites. Column *A* represents the control; *B* and *C* were taken, respectively, immediately and three minutes after the endocardial injury was produced. Following injury there is a definite S-T depression in a lead from the epicardial surface superjacent to the endocardial injury (Row *1*) and definite S-T elevation in leads from the other two epicardial spots (Rows *2* and *3*). This experiment also shows the typical quick restitution found with subendocardial injury which contrasts with the longer persistence of injury effects after epicardial injury. The injury effects are almost entirely gone in three minutes (Column *C*). Discussed in text.

In the epicardial leads, the changes in S-T following subendocardial injury of one side of the interventricular septum were as follows: Injury of the right side of the interventricular septum produced slight elevation of the S-T segment of the right anterior ventricular wall as well as in the right ventricular cavity,

and slight depression of the S-T segment of the anteroapical epicardium of the left ventricle as well as in the left ventricular cavity. Conversely, injury of the left side of the interventricular septum caused an elevation of the S-T segment in leads from the epicardium of the left ventricle as well as from the left ventricular cavity, and a depression of the S-T segment at the anterior epicardium of the right ventricle as well as in the right ventricular cavity.

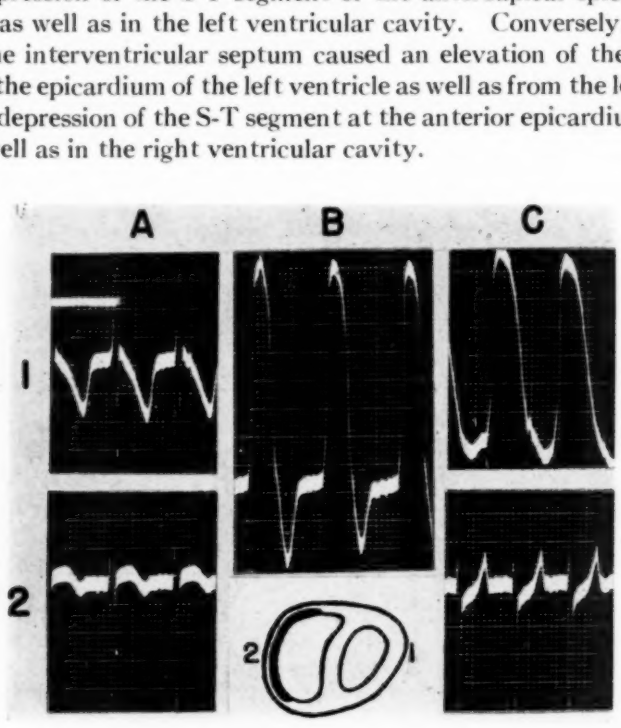

Fig. 11.—Effect of extensive subendocardial injury (by scrape) of the entire anterolateral wall of the right ventricle. The area at necropsy measured 3.0 by 5.0 centimeters. Arrangement of figure as in Fig. 7. Diagram shows location and extent of injury and position of two exploring electrodes employed: *1* is on the epicardial surface superjacent to the middle of the subendocardial injury; *2*, on the epicardial surface of the lateral wall of left ventricular apex. Rows *1* and *2* show, respectively, the records obtained with the exploring electrodes in these two sites. Column *A* represents the control; *B* and *C* were taken, respectively, immediately and two minutes after the endocardial injury was produced. (No record was obtained for Site *2* immediately after injury.) Following injury extremely marked S-T elevation developed in the lead made at the epicardial surface of the left ventricle (Row *1*) and much less marked S-T depression appeared in the lead made at the epicardium superjacent to the endocardial injury (Row *2*). Thus, the injury effects were more marked in this case on the opposite uninjured ventricle, at which site a huge monophasic ventricular complex appeared. Ventricular fibrillation occurred three minutes after the records of Column *C* were obtained. Discussed in text.

VI. Effect of Transmural Injury on Epicardial and Intracavity Leads.—

Incomplete Transmural Injury: The entire thickness of the ventricular wall was injured in four animals, but in these, normal muscle was found to be present, interspersed with the injured muscle. The results in the four experiments were similar.

In one of these animals, subendocardial injury was first produced by alcohol injection, and later injection of an additional amount led to S-T elevation in the overlying epicardium as well as within the cavity itself (Fig. 17, lower right hand diagram). Post-mortem examination revealed the entire thickness of the wall in the region of the injection to be mottled yellowish gray with minute reddish brown areas of normal-appearing myocardium. This indicated that some normal subendocardial muscle was present.

In three animals an area of cautery injury was produced. For example, in one of these the injury was on the anterior wall of the right ventricle. The record from the right intracavity lead showed a decreased size of the QS, an upward displacement of the S-T segment, and a deeply inverted T wave. Recovery was complete in fifty-five minutes. Post-mortem examination revealed an area of injury 2.0 cm. in diameter, with necrosis of the subepicardial muscle to a depth of 1.0 mm. and hemorrhage in the subjacent subendocardial muscle, portions of which appeared normal.

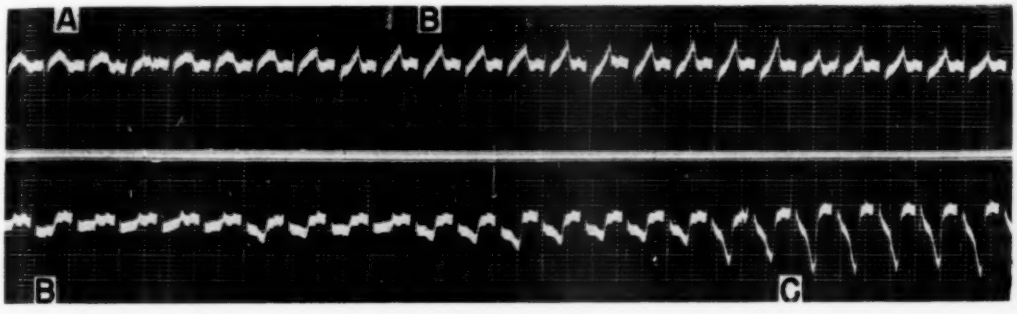

Fig. 12.—Electrical changes occurring at the epicardium superjacent to a subendocardial injury (by scrape) of the anterior wall of the right ventricle (injured area, 1.0 cm. in diameter). The two strips show a continuous record obtained by shifting the exploring wick electrode from a point (*A*) 1.0 cm. away from the edge of injury toward the injured area (between points labelled *B*) and to a point 1.0 cm. beyond the injury (*C*). The S-T segment is isoelectric at *A*, becomes depressed over *B*, and this depression lessens at *C*, tending to approach the isoelectric level at the end of the strip. The T-wave contours in this figure are similar to those seen in the several regions before injury was produced and are, therefore, not attributable to the subendocardial injury. Discussed in text.

Complete Transmural Injury: In two animals heat coagulation of a large area (2.5 by 5.0 cm.) of the anterior wall of the right ventricle (Fig. 14) was produced by holding a red hot soldering iron firmly against it for two minutes. Surprisingly, the heart continued to beat regularly. A continuous record was obtained from a subjacent electrode within the right ventricular cavity while the injury was produced (Fig. 13, *A*, *B*, and *C*). The changes were slight. The T wave became slightly smaller. No QS or S-T alterations were noted. An unusual notching appeared on the T wave in the intracavity lead which disappeared in four to five minutes (Fig. 13,*C*). An epicardial lead from the center of injury revealed complexes identical with those from the right cavity lead (Fig. 13,*D*, last strip), although electrical alternans (of the S-T segment and T wave) appeared. In the second animal an electrical alternans involving only the S-T segment and T wave was observed (Fig. 13,*E*). This preceded spontaneous ventricular fibrillation. Epicardial leads from uninvolved portions of the right ventricle in this animal and from the anterior left ventricle showed no significant S-T deviation.

The results in these two animals indicate that total destruction of the entire area of injury produces a "hole" through which the epicardial electrode "drains" the intracavity potentials.

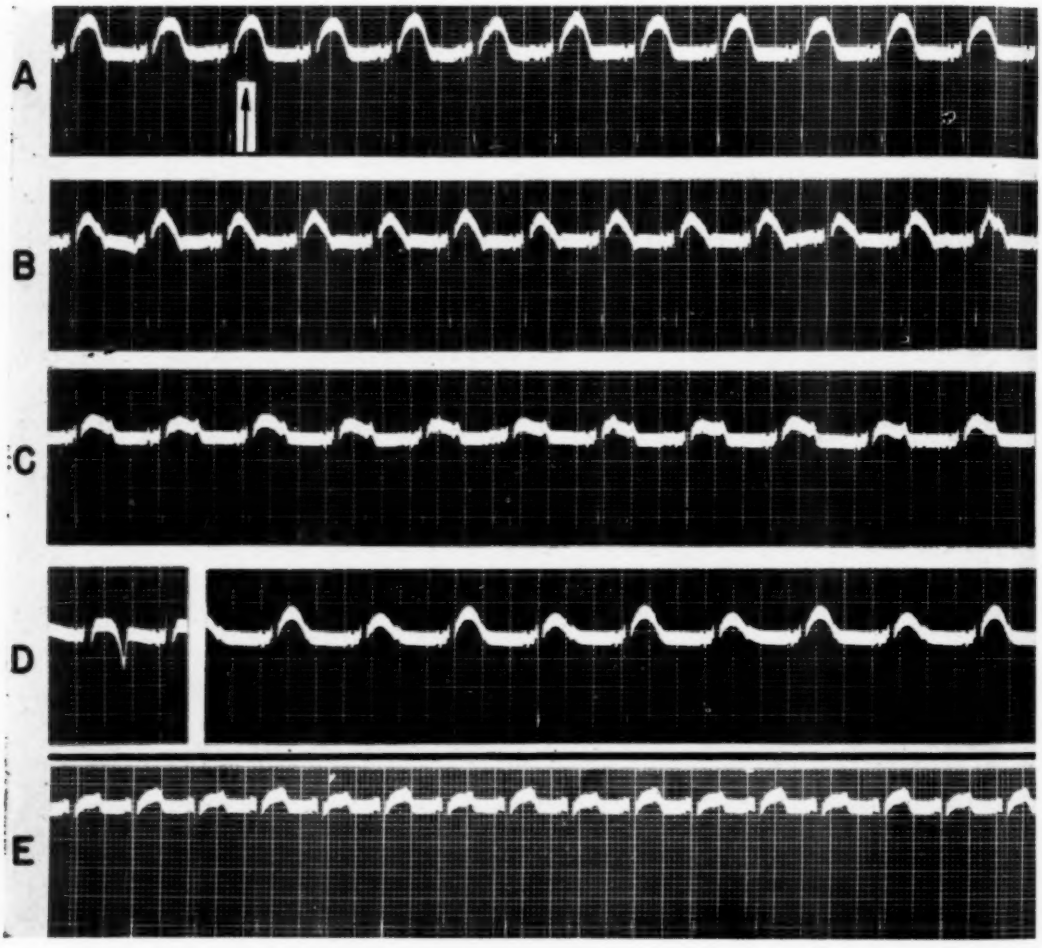

Fig. 13.—Electrical changes occurring in the right ventricular cavity and at the epicardium superjacent to an extensive transmural injury of the anterior wall of the right ventricle produced by burning an area 2.5 by 4.2 cm. on the epicardial surface with a soldering iron. Post-morten examination (*Fig.* 14) revealed damage through the entire thickness of the wall.

A, *B*, and *C* are from a continuous strip obtained with an exploring electrode in the right ventricular cavity subjacent to the injury. The arrow in *A* indicates time at which injury was produced. It will be seen that this extensive injury produced no change for twelve seconds. In *B*, T has become smaller and is diphasic (±). Seventy-two seconds later when *C* was taken, T has become notched. However, no S-T deviation was produced by the injury at any time.

D shows the effect of this extensive injury upon the record obtained with an exploring electrode on the epicardium over the center of injury. The first segment is the control; the second segment was taken ninety seconds after the injury was produced. Note the similarity of the epicardial record, after injury, to the intracavity tracing. Also note the appearance of an electrical alternans involving the ST-T complex. Ventricular fibrillation occurred ten minutes later.

E shows another instance of electrical alternans involving the ST-T complex, obtained in another preparation with a right intracavity electrode following extensive injury of the right side of the intraventricular septum. Discussed in text.

In another animal, the intracardiac electrode was inadvertently pushed through the apex of the right ventricle. No injury effects were noted in the right intracavity lead or in epicardial leads, even when the exploring electrode was within 2.0 mm. of the hole.

Fig. 14.—Photographs illustrating post-mortem appearance of transmural char injury of the right ventricle, the preparation from which tracings *A*, *B*, *C*, and *D* of Fig. 13 were obtained. Black area represents the charred region. Upper picture shows the epicardial surface; lower picture, the endocardial surface.

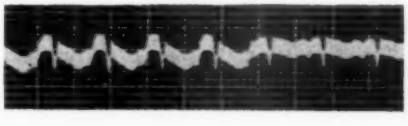

Fig. 15.—The electrical changes occurring at the endocardium superjacent to a subendocardial injury of the right atrium produced by the exploring electrode (by pressure). Electrode pressure was begun before the record was taken and was released before the third from the last beat of the record. Note that during injury the P-Q (P-T_A) segment is elevated and that following release it returns to the isoelectric level. Discussed in text.

VII. Effect of Intramural Injury on Epicardial and Intracavity Leads.—In one animal a pure intramural injury without involvement of the subendocardium or subepicardium was successfully produced in the anterior wall of the left ventricle by alcohol injection. After the needle was inserted and the position of its tip determined, a control record was taken from the superjacent epicardial surface. The minimal S-T deviation which developed subsided in less than ten minutes. Then 0.5 c.c. of 95 per cent alcohol was injected. No injury effects were found in the epicardial and intracavity leads (Fig. 17, lower right hand drawing). Autopsy confirmed the purely intramural position of the injury. In this same animal other parts (subendocardial and subepicardial) of the left ventricle were later injected with alcohol and the expected injury effects appeared. Apparently, therefore, the lack of change in purely intramural injury is to be attributed to the absence of subepicardial or subendocardial involvement.

In two other animals in which such injury was attempted, it was found, post mortem, that the injury had extended to the epicardium.

VIII. Miscellaneous Observations.—It was noted that a Q wave appeared in epicardial leads following injury only in those instances in which there was morphologic evidence at necropsy that the injury was complete and transmural. This Q wave was not found outside the area of injury.

Records made from the epicardial surface of the left ventricle while the subendocardium of the right ventricle was being injured revealed many instances of premature beats in which the peak of the R wave was relatively late. This finding is compatible with the idea that the beat originated at the site of injury. A simliar late occurrence of the peak of R was seen in premature beats recorded from the epicardium of the right ventricle during injury of the subendocardium of the left ventricle. This is interpreted in the same way.

Subepicardial injury led to a significantly longer duration of the injury effect than occurred with a similar injury to the subendocardium.[11,13] Furthermore, injury of the subepicardium produced a greater injury effect than a similar amount of injury to the subendocardium. The lesser effect and shorter duration of subendocardial injury may depend upon the constant lavage of the injured endocardium and subendocardial myocardium by the blood coursing through the heart cavities and leading to dissipation of the products of injury.[13] In clinical subendocardial injury the endocardium is usually intact, so that the injury effect would be expected to persist for a longer period of time.

It was found that the sensitivity of various parts of the endocardial surface of the ventricles in producing ventricular fibrillation varied greatly. Injury of the posterobasal part of the interventricular septum and of the papillary muscles of the left ventricle most readily led to ventricular fibrillation.

Intracavity electrodes remained in situ for eight or more hours without the formation of intracardiac thrombi. In only three of thirty-one animals was there any evidence of trauma due to the presence of the intracardiac electrodes. Localized subendocardial hemorrhage was found in these cases at the junction of the superior vena cava with the right atrium. This is attributed to the protracted irritation by the electrode rod. No change in cardiac rhythm was caused by this atrial hemorrhage.

After opening the pericardium with minimum handling of the heart, the T waves in the control record obtained with direct epicardial electrodes were found to be inverted, a phenomenon previously discussed by Pruitt and associates,[11] Smith,[12] and Byer and associates,[13] and attributed by them to the effect of cooling on repolarization. In intracavity leads the T waves were upright when the chest was opened. However, in the animals with closed chests the T waves were inverted in the right intracavity lead.

DISCUSSION

The results of these experiments can be readily explained by a logical extension of the classical membrane theory as applied to a heart immersed in an extensive conducting medium.

The classical membrane theory postulates that the atria and ventricles are each a syncytial cell bounded by a semipermeable membrane. In the resting state the cell surface is polarized with an equilibrium existing between the positive charges on the outside and the negative charges on the inside of the surface. During activation of the cell the polarized state at its surface is destroyed. This does not happen simultaneously in all parts of the cell, but develops asynchronously with a typical topographical spread. When all parts of the cell are activated the cell surface is completely depolarized and, as in the polarized state, all parts of the cell surface are at the same potential. After a brief time the polarized state is restored to the cell surface. Repolarization, like depolarization, is not simultaneous in all parts of the cell, but has a typical topographical distribution which ordinarily is different from that taking place during depolarization.

When the cell is in an extensive conducting medium it can be shown that during depolarization and repolarization a hypothetical surface at the junction between depolarized and polarized portions of the cell can adequately account for the electrical field created in the medium. The series of doublets lining this theoretical surface can depict the origin of the electrical field. The negative poles of these doublets are on the side of the surface toward the depolarized portion of the cell while the positive poles are toward the polarized portion of the cell, and the intensity of the charge on the theoretical surface is equal to the intensity of the charge on the polarized part of the cell surface. This concept, first developed by Lewis,[18] was amplified by Craib,[19] Ashman and associates,[20] Bayley,[21] and others[28] and has been most clearly ennunciated by Wilson and co-workers.[22] Further details can be obtained by reference to Wilson and co-workers[22] and to Katz.[10]

When the myocardium is injured the simplest effect is that the surface membrane in the region of injury is destroyed or depolarized. The polarized surface membrane of the uninjured part of the resting syncytial cell no longer forms a closed surface. In an extensive conducting medium an electrical field is established which can be accurately portrayed by assuming a theoretical surface at the junction between the injured and uninjured parts of the cell. The intensity of the charge on this theoretical surface is the same as that on the surface of the

uninjured part of the cell. The charges on this theoretical surface are oriented so that the negative charges face the injured part and the positive charges face the uninjured part of the cell. This would be the state of affairs during the resting period of the uninjured part of the cell. A current of injury will therefore flow during rest, having as its apparent source that aspect of the theoretical surface adjacent to the uninjured part of the cell and as its apparent sink that aspect of the theoretical surface adjacent to the injured part of the cell. This current of injury will flow as long as the uninjured part of the cell remains polarized. When the cell is completely activated and its uninjured surface is completely depolarized, the current of injury will disappear, only to reappear when the cell surface of the uninjured part begins to repolarize. This has, therefore, been called an injury current of rest. In this situation the S-T segment would not be displaced from the isoelectric level, only the T-R segment.

Other possibilities following injury have been postulated by Eyster and associates,[23,24] by Ashman and co-workers,[20] and especially by Katz and associates.[10,14] For example, the injured part of the cell may not be depolarized by injury but may become unresponsive during activation. Hence, during the resting stage of the cell no injury current will occur because all parts of the cell have the same polarized state. Thus, no injury current of rest appears. However, during activation all parts of the cell, except that which is injured, will be depolarized so that during activity a theoretical surface may again be depicted at the junction between injured and uninjured parts of the cell, with the charges so arranged that the positive charges are adjacent to the injured part and the negative charge adjacent to the uninjured part. This will give rise to an injury current of activity. In this situation there would be an S-T deviation from the isoelectric level but no T-R displacement.

Another possibility which can occur following injury[14] is that the injured region is partially depolarized and, at the same time, becomes unresponsive. Under these circumstances there would be an injury current of rest, oriented, as in the case already outlined, where the injured part of the cells was assumed to be completely depolarized, but it would be of smaller magnitude. In addition, however, there would also be an injury current of activity, oriented as in the case where the injured part of the cell was assumed to be completely polarized but unresponsive, but it too would be of smaller magnitude. In this situation there would be both an S-T displacement and an opposite T-R displacement from the isoelectric level, the magnitude of each being dependent, respectively, on the extent of depolarization of the injured part during rest and the completeness of the unresponsiveness of the injured part during activation.

In the present experiments the validity of these possibilities was clearly established both for subepicardial and subendocardial injury. The experiments were carried out with exploring electrodes on the injured part, on the superjacent uninjured part, and at distant points both in the cavities of the ventricles and on the epicardial surface of the heart. In Fig. 19,*B*, *C*, and *D*, these three possibilities are diagrammatically represented, and in Fig. 16 the actual time evolution of typical experiments, as far as S-T and T-R displacement are concerned, are shown. For example, it was found that in records from the injured area produced

by the endocardial pressure injury, instances were found in which the T-R segment showed marked depression with the S-T segment showing little elevation from the isoelectric line. In other experiments, equal displacement in opposite directions of the S-T and T-R segments appeared, and in some experiments the S-T displacement was marked while the opposite T-R segment displacement was slight.

In previous reports from this laboratory,[10,14] another effect of injury was postulated: an effect upon the repolarization process. This was called the injury current of repolarization. In such circumstances, whether or not the injured part of the cell was partially depolarized, it was assumed that injury could retard the repolarization of the injured part of the cell, provided that it was at least partially responsive. The T waves following injury were accounted for in this way. In the present experiments, the injury current of repolarization ordinarily appeared at a different time or in a different location from that of the injury current of rest and/or activity, confirming the earlier work of this laboratory.[14] This injury current of repolarization appeared not only with subepicardial injury but with subendocardial injury as well. The well-established fact that "coronary" T waves, representing, we believe, injury currents of repolarization, occur later than injury currents of rest and/or activity was clearly confirmed in these experiments. In addition, several instances were found in which the injury current of repolarization preceded the injury current of activity and/or rest. This confirms the observation of Bayley and co-workers[25] that "coronary" T waves may precede the S-T deviations. However, our interpretation of this phenomenon differs from that offered by Bayley and associates.

Obviously, when the injured part of the cell is completely depolarized or unresponsive it will not contribute to the electrical field created during activation. This lack of response of the injured part is responsible for the alteration of the QRS complex found with injury. Our present experiments have confirmed the presence of such QRS changes. When, however, the injured region is not completely depolarized and remains responsive, it is possible that injury may lead to prolongation of the depolarization in the injured area when it is activated and thus produce prolongation of QRS. Such prolonged QRS complexes during injury, with the associated and expected alterations in the S-T segment and T wave, were found on several occasions following subendocardial injury in regions confined to the neighborhood of the injury. It appears, therefore, that in these experiments we have demonstrated injury effects during depolarization which, by retarding the process of depolarization in the region of injury, lead to prolongation of QRS limited to exploring electrodes in the immediate neighborhood of injury. We have called this *local focal intraventricular block*. In the presence of extensive areas of injury this local focal intraventricular block might possibly lead to prolongation of QRS, even in more distant leads.

The direction of the displacement of the S-T segment and T-R segment found in these experiments can be explained logically on the spatial orientation of the exploring electrode in relation to the region injured. While no precisely quantitative orientation between the electrode and the theoretical charged surface postulated at the junction of the injured and uninjured areas can be made

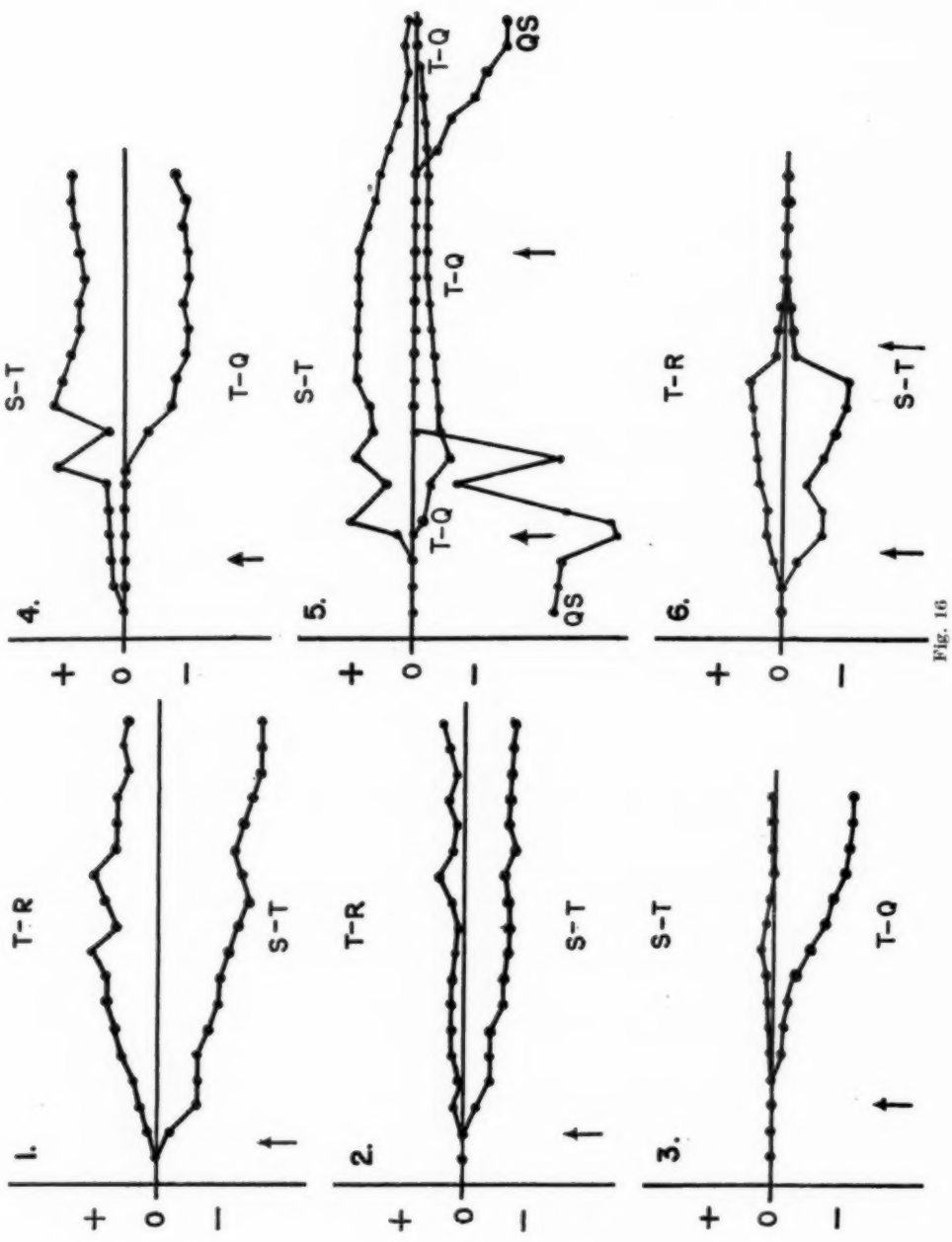

Fig. 16

Fig. 16.—Six charts constructed as in Fig. 2 of a previous communication[14] to show the extent and time course of the S-T and T-R (T-Q) displacements following injury in the several experiments. In each case, the arrow indicates when injury was induced. In Charts *5* and *6* two arrows are shown, the second one indicating the time of release of compression injury; these charts thus show also the effects of recovery from injury. The S-T and T-R (T-Q) displacements are recorded for each beat from continuous records plotted in millimeters against time. The cycle lengths of Graphs *1* to *6* are

(*Legend continued on opposite page.*)

on the basis of the solid angle subtended from the exploring electrode to the theoretical surface, nevertheless, the directional changes found show no exception from the expected rules, other than that found when the exploring electrode was close to the edge of the injured region.

The true displacement caused by injury of the S-T and T-R segments can only be obtained by a continuous record while injury is produced. In this situation the reference level for displacement is the isoelectric level found before injury is produced. Ordinary records taken at intervals after injury will not reveal whether it is the S-T, or T-R, or both, which have been displaced. Under these circumstances, the T-R displacement, as well as other constant currents, is neutralized by the introduction of oppositely directed compensatory currents, and there is no way of distinguishing the injury current of rest from these other constant currents. Hence, the T-R displacement will remain unrecognized as such and will be manifest as an opposite displacement of S-T, since during complete depolarization the injury current of rest is no longer flowing and the introduced compensatory current is unbalanced. The S-T displacement is judged from the T-R level which in interrupted records is taken as the isoelectric level.

With the exception of the case of the electrode close to the edge of injury, which will be discussed later, the rest of the findings follow simple rules. If a plane is constructed parallel to the surface of the heart upon which the injury was produced so as to fall on the junction of the injured and uninjured regions, then all points on the side containing the injured area will show an elevated S-T segment and/or a depressed T-R segment while all points on the opposite side of this plane will show the reverse deviation of the S-T and T-R segments. The data shown in the actual experiments, notably Figs. 7, 8, 9, 10, and 11, as well as the summary charts in Fig. 17, will show this to be true. This is summarized schematically in Fig. 18. The foregoing proposition was found to pertain both to subepicardial injury and to subendocardial injury. Strikingly enough, the effects on the S-T segment and T-R segment of subendocardial and subepicardial injury of the same part of the wall of the ventricle gave exactly opposite

---

respectively, 0.34, 0.36, 0.30, 0.28, 0.52, and 0.28 second. The zero line represents the isopotential level at the site of the exploring electrode determined before injury was induced.

In Chart *1*, the injury was subepicardial and located on the posterior wall of the left ventricle (topical potassium chloride) and the exploring electrode was on the epicardium of the anterior wall of this ventricle. The S-T depression produced was greater than the T-R elevation.

In Chart *2*, the injury was a subepicardial one on the lateral apical region of the left ventricle (topical potassium chloride) and the exploring electrode was in the right ventricular cavity. The S-T depression produced was more marked than the T-R elevation.

In Chart *3*, the injury was a subendocardial one on the anterior wall of the right ventricle (pressure electrode) and the exploring electrode was therefore over the injury. No significant S-T deviation was produced but a definite T-R (T-Q) depression developed.

In Chart *4*, the experimental conditions were the same as in Chart *3*. Here, however, the S-T elevation produced was of the same extent as the T-R (T-Q) depression.

In Chart *5*, the experimental conditions were the same as in Chart *3*. Here, however, the S-T elevation produced was greater in extent than the T-R (T-Q) depression. A monophasic ventricular curve developed and QS disappeared, as indicated. With release of the pressure, the S-T, T-R (T-Q), and QS tended to return to their control values.

In Chart *6*, the injury was located and produced as in Charts *3*, *4*, and *5*. However, the exploring electrode in this instance was located on the epicardium superjacent to the subendocardial injury. The direction of S-T and T-R displacement is the reverse of that occurring in the preceding three graphs. The S-T depression is a little greater than the T-R elevation. Complete recovery occurred within two beats following release of the pressure on the endocardium. Discussed in text.

effects on exploring electrodes, whether these were in the cavities of the heart, on the adjacent or distant epicardial surfaces, or on the adjacent endocardial surface. Furthermore, subendocardial injury on the right side of the septum gave rise to effects in intracavity and epicardial exploring electrodes opposite to those obtained with injury to the left side of interventricular septum. When the exploring electrode came to lie in the projection of the plane between the injured and uninjured regions parallel to the wall of the ventricle involved, then

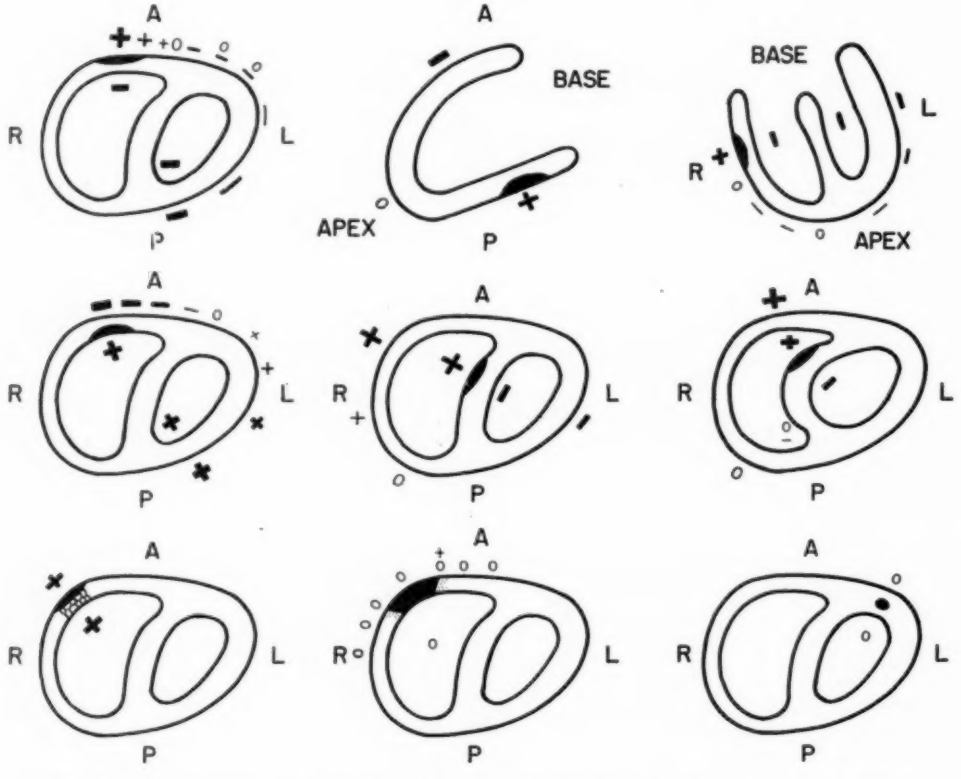

Fig. 17.—Diagrammatic representation of the effect of injury in various locations on the S-T displacement. The blackened area in each of the nine figures locates the injured area. Stippling indicates regions of injury intermingled with uninjured regions. Network indicates extension of hemorrhagic regions beyond injury. Plus (+) means S-T elevation; zero (0), isoelectric S-T; minus (—), S-T depression: the thickness of plus and minus signs gives an index of the relative magnitudes of the S-T deviations. *A* is anterior; *P*, posterior; *R*, right; and *L*, left. Discussed in text.

no S-T or T-R displacement occurred. This was true for subepicardial and subendocardial injury and was true whether the latter was of the interventricular septum or the outer wall of the ventricles. Furthermore, the magnitudes of the S-T and T-R deviations reached their maxima when the exploring electrode distant from the injury was situated at an angle normal to the plane of the injured ventricle. Wilson and associates[22] have stated the principle of this concept in these words: "If the injured fiber is immersed in an infinite medium, the potential of any point P within the medium will be ϕW where W is the solid angle sub-

tended by the region of injury. If the medium is transparent and the muscle opaque, the potential of all points from which the injured region is visible will be negative, and that of all other points will be positive (during diastole)."

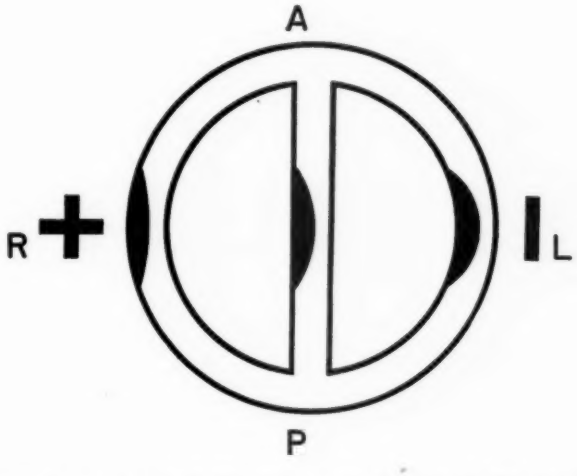

Fig. 18.—Schematic recapitulation of findings. Conventions as in Fig. 17. Shown are subepicardial injury of the right lateral wall, subendocardial injury of the right side of septum, and subendocardial injury of the left lateral wall. If the figure is rotated 180° and *P* and *A*, and *R* and *L* are reversed, the effect of three other injury locations will be illustrated, namely, of the subepicardium of the left lateral wall, of the subendocardium of the left side of the septum, and of the right lateral wall. Discussed in text.

To illustrate this point (see Fig. 18), upward displacement of the S-T segment will occur when the exploring electrode overlies an area of subepicardial injury, when the electrode is placed in the cavity or on the epicardial surface of the ventricle whose interventricular septal subendocardium is injured, or when the exploring electrode is within the heart cavities or on the epicardial surface of the wall of the ventricle opposite to that containing a subendocardial injury. Conversely, downward displacement of the S-T segment will occur when the exploring electrode is on the epicardial surface overlying a subendocardial injury, when the exploring electrode is within the cavity or on the epicardial surface of the ventricle opposite to that containing a subendocardial injury of the interventricular septum, or when the exploring electrode is on the epicardium of the wall of the ventricle opposite to that containing a subepicardial injury.

The situation may be summarized differently. A vector may be used to represent the *effect* of injury. It would appear to be directed at right angles to the surface injured and have its negative and positive poles arranged so that during the activated state the former would appear to be on the side having the junction of injured and uninjured regions and the latter, the junction of injury with the surface of the heart, whether this be epicardium or endocardium. In this way S-T elevation will be present on that side of the injury which surfaces on the heart and S-T depression on that side of the injury which adjoins uninjured tissue, since (by construction) an electrode which is in a relatively positive

electric field will record an upward deflection and an electrode which is in a relatively negative electrical field will record a downward deflection. The situation for an injury current of activity is self-evident. In the case of an injury current of rest, this orientation of the vector comes about because the injury current is neutralized and hence, only the compensatory current is recorded when during the completely activated state the injury current no longer is flowing.

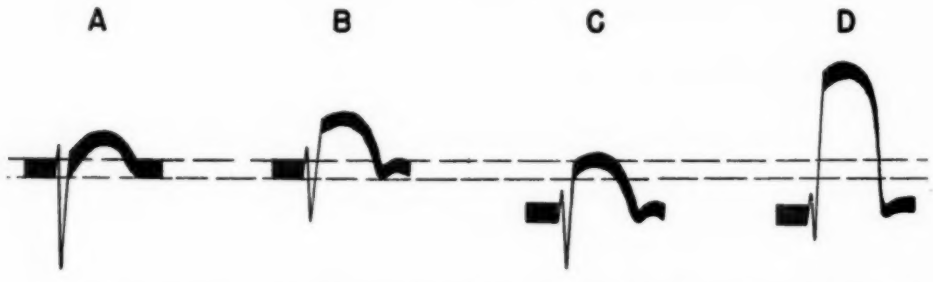

Fig. 19.—Schematic representation of the three types of injury effects found in leading from a subendocardial injured area produced by a pressure electrode. These are similar to those described for subepicardial injury.[14] The dotted line represents the isoelectric level determined from the control record, *A*. This control record is from the tip of the right ventricular cavity. *B*, *C*, and *D* represent curves after injury. In all, the S wave becomes smaller. In *B*, the development of an injury current of activity is depicted; this causes the S-T segment to be elevated. In *C*, the development of an injury current of rest is depicted; this causes the T-R (T-Q) segment to be depressed. In *D*, the development of both an injury current of rest and an injury current of activity is depicted; this causes both elevation of S-T and depression of T-R (T-Q). Such changes are obtained only in continuous records, started before injury is made; the control record serves to locate the isoelectric level from which S-T and T-R (T-Q) deviations can be judged. When a large symmetrical T wave appears, it is inverted; it represents an injury current of repolarization. Discussed in text.

These simple rules must be modified when the exploring electrode is in the neighboring epicardial surface surrounding a subepicardial injury. Here the theoretical surface between injured and uninjured areas cannot be considered as a single unit but must be broken down into its component parts. With a subepicardial injury that is extensive, most of the theoretical surface between injured and uninjured surfaces will be parallel to the surface of the heart, but at its edges the theoretical surface will come to lie progressively more perpendicular to the heart surface. When the exploring electrode is in the neighborhood of the injury it will be at an unequal distance from various parts of the theoretical surface between injured and uninjured areas. Hence, the more distant part of this surface will have a significantly less marked effect, depending upon the extent of the injury. As a rough approximation it may be considered that only that part of the theoretical surface close to the electrode affects its potential when the electrode is near one edge of the injury; this might be called an intrinsic effect. Take the simplest situation, that of a case with only injury current of rest. The part of the theoretical surface close to the electrode is at right angles to the surface of the heart with its positive charge in the uninjured side and its negative charge on the injured side. When the exploring electrode is over the injured area the S-T segment will be displaced upward, but as the exploring electrode is moved over to the uninjured region, even though it be on the same wall as

that which has been injured, the S-T segment becomes isoelectric, and in more distant regions on the same wall, it becomes depressed. This confirms the original observation of Wilson and co-workers.[22] Thus, in a complete experiment such as is diagrammatically depicted in the upper right-hand diagram of Fig. 17, there will be two zones of isoelectric S-T segments on the epicardial surface of the heart: The first, in the immediate neighborhood of the injured area, is due to the predominant effect of that part of the theoretical surface which is closest to the exploring electrode; the second, occurring while the electrode is moved from the wall upon which the injury is located to the opposite wall, is due to spatial orientation of the exploring electrode to the major aspect of the theoretical surface.

It is significant that the effects of subendocardial injury on superjacent endocardial or intracavity electrodes are remarkably similar to those of subepicardial injury on superjacent epicardial electrodes. This is not unexpected since injury in either location causes similar effects. The use of the endocardial pressure electrodes and the intracavity catheter electrodes in our experiments has helped to clarify the role of the subendocardial myocardium in the genesis of the electrocardiogram. There can be no question from our results that the subendocardium is not electrically silent, as suggested by some investigators.[4,11]

Our experience with transmural injury shows that less change occurred in the subjacent intracavity electrode than with slight superficial subepicardial injury in other experiments. Total death occurred in these transmural injuries as demonstrated by the tracings taken with the exploring electrode on the epicardial surface at the center of the injury. The record so obtained was almost identical with that obtained from within the cavity, suggesting, following Wilson and associates,[26] that a new "window" has been opened into the cavity of the heart. In clinical myocardial infarction, the QS obtained in chest leads lying over the area of infarction has been explained in similar fashion. The argument is based on the fact that a QS is frequently observed when the chest electrode is at the C_1 position and in the V_R lead. The exploring electrodes in these two situations have a spatial orientation which permits them "to look through the normal window of the ventricle," the A-V opening, and so pick up the same type of record as can be obtained within the cavities of the heart during activation. If this argument is correct, then the complete transmural injury produces a tubular "hole" in the ventricle with negative charges on its inside and positive charges on its outside. On both the endocardial and epicardial surfaces, these charges would tend to neutralize each other and hence no S-T deviation might be expected. If the transmural injury were larger, then S-T elevation might be expected on the epicardial surface for two reasons: (1) The injured area would be conical with its greater diameter on the epicardial surface so that the theoretical surfaces would face outward; and (2) when the exploring electrode is closer to one edge than the other, that edge will have a dominant influence as in the case of a subepicardial injury.

With incomplete transmural injury, upward S-T displacement was recorded both with a subjacent intracavity electrode and with an epicardial electrode over the injury. The epicardial effects can be explained as being due to a

laminar subepicardial injury, while the intracavity effects can be explained by discrete subendocardial injury.

When a purely intramural injury was produced which did not surface on the epicardium or endocardium no injury currents were obtained. This is not unexpected since the theoretical surface between injured and uninjured areas would constitute a complete sphere or at least a completely enclosing three-dimensional surface and the charges on this surface would neutralize each other completely.

The results of our experiments are for the most part in accord with those obtained in the excellent study of Wolferth and co-workers.[3] The suggestion made by Wolferth and his colleagues that the S-T displacement can be classified as primary and secondary is in our opinion neither valid nor necessary. We have shown that the direction of the S-T displacement depended purely upon the spatial orientation of the exploring electrode in relation to the theoretical surface between injured and uninjured areas, except that when the exploring electrode is near the edge of the injury, it will depend upon its relationship to the theoretical surface closest to it. This has been discussed in detail and various combinations of injury location and exploring electrode position confirming our explanation have been amply illustrated.

The results of our experiments may have a bearing on the interpretation of the S-T segment displacement in precordial leads in man. Thus, with an anterolateral infarct, marked S-T depression may be found in the C_2 position and increasing S-T elevation may appear in the C_4, C_5, and C_6 positions overlying the injury. This is analogous to electrodes placed, respectively, outside and over a subepicardial injury in our experiments. Again, with an anteroseptal infarct extending to the left side of the interventricular septum, S-T depression may appear in the C_1 and C_2 positions with S-T elevation in the C_4, C_5, and C_6 positions. This is analogous to subendocardial injury of the anterior wall of the left ventricle. Furthermore, the realization that S-T elevation in precordial leads can occur as a result of subendocardial injury of the wall of the heart may explain occasionally atypical posterior wall infarctions which produce typical changes in the limb leads but unexpected S-T elevation in one or more of the precordial leads despite the fact that the infarct does not extend anteriorly. We are convinced that other situations with atypical combinations of S-T changes in precordial leads may be explained along the lines developed in this report.

Our present study offers a reasonable explanation for the contradictory effects reported previously by this laboratory[27] following injury to the various walls of the left and right ventricles. It is possible that during these early experiments the injury produced was in some instances epicardial; in others, endocardial; and in still others, purely intramural. Unfortunately, the location of injury to the epicardium and endocardium was not noted at that time. It is not only the location of the injury on a certain wall of the ventricle which is important but also the fact of whether it is subendocardial, subepicardial, intramural, or transmural.

SUMMARY

1. When an exploring electrode was placed on an area of subepicardial injury (the indifferent electrode being on the left hind paw), an upward S-T displacement occurred; a downward S-T displacement was found when the exploring electrode was placed on the marginal zone surrounding the area of injury. When a contact wick exploring electrode was moved from the area of injury to surrounding uninvolved tissue and continuous records made, a narrow transitional zone was found in which the S-T segment was isoelectric. In regions removed from the area of injury an exploring electrode showed the S-T segment to be slightly depressed or isoelectric in the surrounding epicardium on the same side as the subepicardial injury, depending upon the extent of the injury. When the exploring electrode was on the epicardium of the wall opposite to that injured, downward S-T displacement occurred which was maximal when the exploring electrode was on the axis normal to and intersecting the center of the plane of the area of injury. In passing from the wall injured to the opposite wall a zone in which the S-T segment was isoelectric was found.

2. While the area of upward S-T displacement was confined to the area of injury at the time of injury, with the passage of time S-T elevation extended to surrounding regions on the same wall. At all times, however, the S-T segment displacement was greatest over the area of epicardial injury. The spread of injury effects was uneven. The S-T displacement in equidistant points from the injured area were not of the same magnitude nor did they appear at the same time. The injury effects were usually greater in areas toward the base of the heart.

3. The electrical effects produced by subendocardial pressure or scrape injury on endocardial or intracavity exploring electrodes were similar to those produced over the epicardial surface of a subepicardial injury. These included S-T elevation and T-R depression; monophasic ventricular curves were found. Continuous records over the subendocardial injury, made while the injury was produced, revealed three types of injury effects on the S-T and T-R segments: (1) downward displacement of T-R with no or slight upward displacement of S-T, that is, primarily an injury current of rest; (2) slight downward displacement of T-R and marked upward displacement of S-T, that is, primarily an injury current of activity; and (3) most commonly, almost equal downward displacement of T-R and upward displacement of S-T, that is, injury currents of both rest and activity. These changes in S-T and T-R segments disappeared in parallel fashion on recovery from the injury.

4. The production of S-T segment elevation at any part of the epicardial surface of the heart by various methods of injury of the subepicardium was accompanied by S-T segment depression in leads from the cavities of the heart. This pertained also to the atria.

5. Localized injury of the subendocardium (exclusive of the interventricular septum) resulted in S-T elevation in leads from the heart cavities. Epicardial electrodes directly superjacent to the subendocardial injury showed S-T depression. Leads made with epicardial electrodes at distant points on the wall injured showed slightly depressed or isoelectric S-T segments. Epicardial leads taken at points on the wall opposite to that injured showed S-T elevation.

6. Subendocardial injury of one side of the interventricular septum resulted in S-T segment elevation in leads from the ipsilateral cavity and the epicardium of the ipsilateral free wall, and S-T segment depression in leads from the contralateral cavity and the epicardium of the contralateral free wall. The importance of spatial orientation of the electrode to the area of injury was demonstrated by the absence of S-T segment displacement in an intracavity electrode which was located in the tip of the right ventricle, where the upper anterior part of the left side of the interventricular septum was injured by scraping. The septum bulged convexly into the right ventricle, so that the electrode in the tip of the right ventricle lay in a plane which was the extension of that of the major surface of the subendocardial injury.

7. Incomplete transmural injury of the ventricles produced by cauterization resulted in S-T segment elevation in electrodes on the epicardium over this area and within the underlying cavity. However, instantaneous complete transmural injury produced by charring a large area of the anterior wall of the right ventricle produced minimal changes in the S-T segment and QS of the subjacent right intracavity electrode, and the epicardial electrode over the center of the charred area yielded tracings identical to those obtained from the cavity.

8. Isolated intramural injury produced no detectable injury effects in superjacent epicardial electrodes.

9. It was found that elevation of the S-T segment appeared:

(A) When the exploring electrode was placed on the epicardium immediately superjacent to subepicardial injury.

(B) When the epicardial electrode was placed on the ventricular wall opposite to that containing a subendocardial injury. The S-T elevation was greatest when the electrode was approximately 180 degrees away, that is, on the axis perpendicular to and intersecting the center of the plane of the area of injury.

(C) When the epicardial electrode was placed on the lateral wall of the ventricle in the cavity of which a subendocardial injury of the interventricular septum surfaced.

(D) When endocardial and intracavity exploring electrodes were used after injury of the subendocardium of the outer walls of the ventricles and after injury of the ipsilateral side of the interventricular septum.

10. It was found that depression of the S-T segment occurred:

(A) When the epicardial exploring electrode was placed outside of the area of subepicardial injury. However, two transition zones with isoelectric S-T segments were found. One was near the injured area and the other occurred in passing from the wall injured to the opposite one.

(B) When the epicardial exploring electrode was placed superjacent to subendocardial injury.

(C) When intracavity electrodes were used following injury of the subepicardial surface of any part of the ventricles.

(D) When intracavity electrodes were used following injury of the contralateral side of the interventricular septum.

11. Injury also produced T-wave changes. Usually these developed while the S-T deviations were receding or after they had disappeared. Occasionally, the T-wave changes occurred transiently before the S-T deviations developed. These observations confirm the existence of injury currents of repolarization.

Injury of the subendocardium, on rare occasions, produced QRS prolongation in the regions of injury; local focal intraventricular block. This is interpreted as evidence of an injury effect on depolarization.

12. The relation of these results to the modern concept of injury effects in an extensive conducting medium are discussed. The various types of injury effects are developed: namely, injury current of rest, injury current of activity, injury current of repolarization, and injury effect of depolarization; their demonstration by these experiments is shown. The spatial relation of the exploring electrode to a theoretical surface at the junction of the injured and uninjured areas is used to account adequately for the findings.

13. The present results confirm and extend previous observations of this laboratory.

14. The practical value of these observations is considered.

We are indebted to Mrs. B. Lendrum for her assistance in the preliminary experiments.

REFERENCES

1. Hecht, H. H.: Potential Variations of the Right Auricular and Ventricular Cavities in Man, Am. Heart J. **32**:39, 1946.
2. Forsmann, W.: Die Sondierung des Rechten Herzens, Klin. Wchnschr. **8**:2085, 1929.
3. Wolferth, C. C., Bellet, S., Livezey, W. W., and Murphy, F. D.: Negative Displacement of the RS-T Segment in the Electrocardiogram and Its Relationships to Positive Displacement, An Experimental Study, Am. Heart J. **29**:220, 1945.
4. Nahum, L. H., and Hoff, H. E.: The Configuration of Epicardial and Endocardial Extrasystoles in the Chest Leads, Am. J. Physiol. **145**:615, 1946.
5. Kisch, B., Nahum, L. H., and Hoff, H. E.: The Predominance of Surface Over Deep Cardiac Injury in Producing Changes in the Electrocardiogram, Am. Heart J. **20**:174, 1940.
6. Bayley, R. H.: The Electrocardiographic Effects of Injury at the Endocardial Surface of the Left Ventricle, Am. Heart J. **31**:677, 1946.
7. Pirani, C. L., and Schlichter, J. G.: Subendocardial Myocardial Infarct, Ann. Int. Med. **25**:847, 1946.
8. Langendorf, R., and Kovitz, B.: Acute Myocardial Infarction Without Deviation of the S-T Segment in the Electrocardiogram, Am. J. M. Sc. **204**:239, 1942.
9. Price, R. K., and Jones, J. R.: A Case of Subendocardial Infarction, Brit. Heart J. **5**:134, 1943.
10. Katz, L. N.: The Genesis of the Electrocardiogram, Physiol. Rev. **27**:398, 1947.
11. Pruitt, R. D., Barnes, A. R., and Essex, H. E.: Electrocardiographic Changes Associated With Lesions in the Deeper Layers of the Myocardium, An Experimental Study, Am. J. M. Sc. **210**:100, 1945.
12. Smith, F. M.: Effects of Heat and Cold on Ventricles and T Deflection of Electrocardiogram, Heart **10**:391, 1923.
13. Beyer, E., Toth, L. A., and Ashman, R.: Electrocardiographic Changes Induced by Cooling or Warming the Inner Surface of the Dog's Ventricle, Am. J. Physiol. **149**:264, 1947.
14. Sugarman, H., Katz, L. N., Sanders, A., and Jochim, K.: Observations on the Genesis of the Electrical Currents Established by Injury to the Heart, Am. J. Physiol. **130**:130, 1940.
15. Harris, A. S., and Rojas, A. G.: The Initiation of Ventricular Fibrillation Due to Coronary Occlusion, Exper. Med. & Surg. **1**:105, 1943.
16. Beck, C. S., and Mautz, F. F.: Control of Heart Beat by Surgeon, With Special Reference to Ventricular Fibrillation Occurring During Operation, Ann. Surg. **106**:525, 1937.
17. Wiggers, C. J.: Physiologic Basis for Cardiac Resuscitation From Ventricular Fibrillation—Method for Serial Defibrillation, Am. Heart J. **20**:413, 1940.
18. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, 1925, Shaw & Sons, Ltd., pg. 99 et seq.

19. Craib, W. H.: The Electrocardiogram, Privy Council, Med. Res. Council, Spec. Report, Series No. 147, 1930.
20. Ashman, R., Wilde, W. S., and Drawe, C. E.: The Validity of the Electrical Doublet Theory of the Cardiac Action Current, Am. J. Physiol. **128**:547, 1940.
21. Bayley, R. H.: On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease, AM. HEART J. **26**:769, 1943.
22. Wilson, F. N., Macleod, A. G., and Barker, P. S.: The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissue, Ann Arbor, 1933, University of Michigan Press.
23. Eyster, J. A. E., Meek, W. J., Goldberg, H., and Gilson, W. E.: Potential Changes in an Injured Region of Cardiac Muscle, Am. J. Physiol. **124**:717, 1938.
24. Eyster, J. A. E., and Meek, W. J.: Cardiac Injury Potentials, Am. J. Physiol. **138**:166, 1942.
25. Bayley, R. H., La Due, J. S., and York, D. J.: Electrocardiographic Changes (Local Ventricular Ischemia and Injury) Produced in the Dog by Temporary Occlusion of a Coronary, Showing a New Stage in the Evolution of Myocardial Infarction, AM. HEART J. **27**:164, 1944.
26. Wilson, F. N., Johnston, F. D., and Hill, I. G. W.: The Interpretation of the Galvanometric Curves Obtained When One Electrode Is Distant From the Heart and the Other Near or in Contact With the Ventricular Surface. Part III. Observations on the Mammalian Heart, AM. HEART J. **10**:176, 1934.
27. Korey, H., and Katz, L. N.: The Electrocardiographic Changes Produced by Injuries of Various Parts of the Ventricles, Am. J. M. Sc. **188**:387, 1934.
28. Curtis, H. J., and Cole, K. S.: Membrane Action Potentials From the Squid Giant Axon, J. Cell. & Comp. Physiol. **15**:147, 1940.

CIRCULATORY RESPONSES TO SPINAL AND CAUDAL ANESTHESIA IN HYPERTENSION: RELATION TO THE EFFECT OF SYMPATHECTOMY

I. Effect on Arterial Pressure

Robert D. Taylor, M.D., Robert Birchall, M.D.,*
A. C. Corcoran, M.D., and Irvine H. Page, M.D.
Cleveland, Ohio

THE effects of high spinal anesthesia upon arterial pressure and renal circulation of patients suffering from essential hypertension have been described in brief.[1] In most of the patients, induction of anesthesia resulted in a decrease in arterial pressure. On the assumption that the effects on the circulation of high spinal anesthesia were in large measure similar to those resulting from sympathectomy (lumbodorsal sympathectomy and ganglionectomy), we suggested that the response of arterial pressure to high spinal anesthesia might aid in selecting patients for this operation. Caudal anesthesia differs from spinal anesthesia in that it does not paralyze the nerve supply of voluntary muscle, although it does affect preganglionic sympathetic fibers, so that the denervation is more like that of sympathectomy than is that induced by spinal anesthesia. Such considerations led Russek and co-workers[2,3] to the observation that high caudal anesthesia caused a reduction in blood pressure in many patients suffering from hypertension which paralleled the effect on arterial pressure of subsequent surgical sympathectomy. They recommended measurement of arterial pressures during high caudal anesthesia as a guide to the selection of patients for sympathectomy.

The purpose of this report is to examine the relationship between the effect on arterial pressure of high spinal or caudal anesthesia and the effect of subsequent sympathectomy by the procedure of Smithwick.[4]

PROCEDURES

Preoperative and postoperative studies were made in forty-three patients. Spinal anesthesia was induced in twenty-five of these and caudal anesthesia in eighteen.† The brachial blood pressure of each patient was measured in the supine position twice daily during the four to ten days of hospitalization which preceded operation. The levels taken as controls for each patient in this study were the arithmetic means of these readings.

From the Research Division, Cleveland Clinic and the Frank E. Bunts Educational Institute.
Received for publication Aug. 14, 1947.

*Present Address: Ochsner Clinic, New Orleans, La.

†Dr. W. James Gardner, Chief of the Neurosurgical Service of the Cleveland Clinic, performed the sympathectomies upon all of these forty-three patients.

Spinal anesthesia was induced by intrathecal injection of 180 mg. of Spinocain. In all cases, there was anesthesia extending at least to the level of the sixth thoracic spinal segment. Blood pressure was recorded each minute until constant levels were observed. The lowest value was accepted as representing the maximum effect of spinal anesthesia on the blood pressure.

Caudal anesthesia was given by placing a malleable needle into the caudal canal and slowly introducing enough 1.5 per cent Metycaine solution to induce anesthesia up to at least the level of the sixth dorsal spinal segment. The lowest blood pressure level observed during the period of anesthesia was recorded as representing the effect of this procedure upon arterial pressure.

The effect of operation upon blood pressure was evaluated by comparing control blood pressure with measurements made in the supine position two weeks, three months, and six to eight months after operation.

RESULTS

Comparison of Blood Pressure Reduction by Spinal Anesthesia With That Which Followed Lumbodorsal Sympathectomy (Table I).—Spinal anesthesia, which extended to the nipple line, reduced the blood pressure of twenty (80 per cent) of the twenty-five patients to or below 140/90. In two patients, marked reductions of arterial pressure to 145/85 and 155/105 were observed. In three patients, the control levels of 178/138 and 185/140 were not changed by anesthesia.

Two weeks after lumbodorsal sympathectomy, ten of the twenty-five patients exhibited blood pressure levels that differed only slightly from the control values. Three months after operation the degree of hypertension in sixteen cases was not greatly changed from that observed before operation. Six or more months postoperatively, only six patients (24 per cent) had normal blood pressures. It is interesting that five of these six patients were among those whose blood pressures fell to normal after spinal anesthesia, and the other had a blood pressure drop from 190/120 to 155/105.

Reduction of Blood Pressure Induced by Caudal Anesthesia Compared With That Following Lumbodorsal Sympathectomy.—Caudal anesthesia which produced sensory paralysis to the level of the sixth dorsal spinal segment reduced the blood pressure of twelve of eighteen (67 per cent) hypertensive patients to normal levels. Five of the remaining six persons showed blood pressure falls of 20 mm. Hg or more, systolic or diastolic or both (Table II). The other patient showed no change in blood pressure. Two weeks after surgery twelve of these eighteen patients exhibited hypertension similar to that observed before operation. Four had normal blood pressures, and two showed hypertension of a lesser degree than that present before operation. Only four of the eighteen patients (22 per cent) had normal blood pressure levels measured in the supine position three to eighteen months after operation. All of these four patients had normal blood pressure

TABLE I. COMPARISON OF EFFECTS OF SPINAL ANESTHESIA AND SYMPATHECTOMY ON THE BLOOD PRESSURES OF HYPERTENSIVE PATIENTS

NO.	AGE	SEX	CONTROL B.P. MM. HG	B.P. MM. HG AFTER SPINAL ANESTHESIA	2 WEEKS AFTER OPERATION	3 MO. AFTER OPERATION	6 OR MORE MO. AFTER OPERATION	MO. OF OBSERVATION	
1	43	M	185/105	100/80	180/105	162/110	246/134	21	
2	36	F	150/110	130/86	160/90	150/110	170/110	20	
3	49	F	180/90	145/85	180/90	150/100	180/120	17	
4	34	F	220/140	95/75	170/110	190/120	240/140	16	
5	36	M	188/120	180/140	185/110	160/120	174/128	10	
6	44	M	210/120	150/95	140/95	196/140	264/170	11	Died of cerebral hem.
7	33	F	170/110	170/138	180/120	150/110	150/110	17	
8	43	F	220/120	65/40	210/110	180/110	195/125	7	
9	33	F	180/120	120/80	135/90	156/114	180/130	21	
10	40	F	180/100	90/65	130/80	180/120	190/120	27	
11	47	M	190/130	120/80	190/125	170/120	210/140	12	
12	35	M	190/120	110/60	190/122	206/120	180/110	8	
13	30	F	175/100	100/70	110/60	150/96	156/100	6	
14	44	M	210/130	180/130	180/115	220/160	240/140	12	
15	37	F	170/120	110/80	135/95	160/110	160/120	21	
16	37	F	150/100	115/70	140/90	150/84	196/110	17	Died of coronary thrombosis
17	32	M	160/105	100/65	130/90	150/108	150/102	17	
18	39	M	160/100	75/50	145/95	160/104	155/115	10	
19	28	M	180/130	90/30	120/85	120/92	146/100	26	
20	34	F	200/140	120/90	162/115	120/92	130/84	14	
21	26	F	190/120	155/105	135/88	114/80	114/80	19	Ulcerative colitis
22	34	F	170/105	115/78	140/80	110/70	144/84	28	
23	30	F	160/115	95/65	140/90	165/114	138/86	12	
24	31	F	190/125	100/88	175/100	130/84	136/90	20	
25	41	M	175/105	120/80	140/90	120/90	115/70	12	

TABLE II. COMPARISON OF EFFECTS OF CAUDAL ANESTHESIA AND SYMPATHECTOMY ON THE BLOOD PRESSURES OF HYPERTENSIVE PATIENTS

NO.	AGE	SEX	CONTROL B.P. MM. HG	B.P. MM. HG AFTER CAUDAL ANESTHESIA	2 WEEKS AFTER OPERATION	3 MO. AFTER OPERATION	6 OR MORE MO. AFTER OPERATION	MO. OF OBSERVATION
1	37	F	160/100	120/80	150/110	184/120	180/120	7
2	32	F	150/110	100/76	160/110	150/110	150/110	12
3	45	F	160/90	100/60	160/100	190/110	210/110	19
4	35	F	160/110	132/86	180/120	190/130		3
5	47	M	176/110	100/70	135/90	155/105	176/120	13
6	25	M	210/120	170/130	140/100	140/90	210/130	15
7	36	F	180/110	160/110	150/100	180/130	196/120	20
8	44	F	200/130	100/80	205/138	202/140	200/130	12
9	48	F	170/105	156/100	180/100	180/100	190/120	6
10	39	F	190/120	190/120	170/120	190/120	190/120	6
11	37	F	175/114	158/108	140/90	160/110	170/110	7
12	36	F	168/100	140/90	175/105	158/100	160/100	20
13	45	M	190/130	170/110	160/110	230/145	216/130	18
14	40	F	150/90	136/96	135/95	140/98	166/96	5
15	42	F	200/130	100/62	200/130	124/80	144/90	14
16	41	M	145/100	125/75	140/100	110/88	110/88	12
17	43	M	150/90	145/90	150/94	108/84	140/90	14
18	39	M	180/110	145/90	140/90	126/90	130/86	12

levels after caudal anesthesia, as did one of those whose pressure was appreciably reduced below control values after operation. The anesthesia reduced the pressure of the remaining patient to the same degree as did the operation, 210/120 to 170/120.

DISCUSSION

Since the effects on arterial pressure of spinal and caudal anesthesia in hypertensive patients are the same, observations on the two groups are discussed together.

Sympathectomy has at long last become an accepted procedure for the treatment of essential hypertension. The condition of many patients is favorably affected by operation. In our observations, which extend over thirteen years, the majority of patients experience subjective improvement. A minority of about 25 per cent show a sustained reduction of arterial pressure as measured in the supine position. In these latter the benefit of operation is indisputable. Others show a lessening of the severity of vascular disease in spite of continued hypertension.

Clearly the value of surgery in the treatment of hypertension would be enhanced if it were possible to select those patients whose blood pressure could be reduced or those in whom the progress of disease could be arrested. Although many methods of selection have been proposed, none has proved satisfactory. It is unfortunate but true that no single test has yet been found which allows accurate selection. The situation has not changed materially since 1938 when we selected largely at random and came to the pragmatic conclusion that patients with early essential hypertension and with early malignant hypertension had the best chance of obtaining a good result.[5] Occasionally those with advancing essential hypertension also received significant objective benefit.

Spinal and caudal anesthesia have the theoretical advantage over other tests in that their effects on the circulation depend at least in part on the mechanisms affected by sympathectomy. A parallelism of effects on arterial pressure might therefore have been expected. That this is true in some degree is apparent from the fact that ten of the twelve patients whose pressures were normal after operation had attained normal levels during anesthesia and the other two had experienced appreciable falls. However, response of arterial tension to anesthesia parallels the operative result in only one-third of our observations. Twenty-six patients who showed little or no effect from operation had shown a decrease of pressure during anesthesia.

This experience differs from that of Russek and co-workers[3] who found an association between the effect of caudal anesthesia and that of sympathectomy in eleven of twelve observations. The discrepancy may depend upon the number of our observations as compared with theirs. On the other hand, the suggestion is confirmed that those patients who respond unfavorably to preoperative block of the sympathetic fibers by anesthetic agents also respond poorly to operation. Thus, the blood pressure response to spinal and caudal anesthesia has no more than negative value in predicting the end result of sympathectomy.

There remains to be considered why the arterial tension may be greatly decreased by spinal or caudal anesthesia and still persist at preoperative levels when observed weeks or months after operation. In this connection, it should be noted that blood pressure is decreased after operation in nearly every hypertensive patient for periods of hours or days. In a few it persists at a low level, but in most it returns to a level approximating that existing before operation. It may be that the immediate postoperative decrease of pressure corresponds to that seen under anesthesia. The mechanism of this change is considered in a following paper.[6]

SUMMARY

The effects of caudal and spinal anesthesia on arterial pressure in hypertension are similar despite the fact that in the former, voluntary muscles are not paralyzed. During anesthesia marked decreases in pressure were observed in forty of the forty-three patients. Blood pressure was persistently decreased by lumbodorsal sympathectomy and ganglionectomy in twelve of these patients. The three patients whose arterial pressures were not decreased by anesthesia were similarly unaffected by operation.

It is concluded that the blood pressure response to spinal and caudal anesthesia has no more than negative value in the selection of patients for sympathectomy. The discrepancy between the effects on arterial pressure of spinal or caudal anesthesia and sympathectomy may be due to the great difference in time during which the effects are observed or to a difference in the denervation which each of them causes.

REFERENCES

1. Page, I. H., Taylor, R. D., Corcoran, A. C., and Mueller, L.: Correlation of Clinical Types With Renal Function in Arterial Hypertension. II. Effects of Spinal Anesthesia, (Proc. Cent. Soc. Clin. Res.) J. A. M. A. **124**:736, 1944.
2. Russek, H. I., Southworth, J. L., and Zohman, B. L.: Continuous Caudal Anesthesia as a Test in the Selection of Hypertensive Patients for Sympathectomy, J. A. M. A. **128**:1225, 1945.
3. Russek, H. I., Southworth, J. L., and Zohman, B. L.: Selection of Hypertensive Patients for Sympathectomy, J. A. M. A. **130**:927, 1946.
4. Smithwick, R. H.: A Technic for Splanchnic Resection for Hypertension: Preliminary Report, Surgery **7**:1, 1940.
5. Page, I. H.: Medical Aspects of Surgical Treatment of Hypertension, J. A. M. A. **110**: 1161, 1938.
6. Corcoran, A. C., Taylor, R. D., and Page, I. H.: Circulatory Responses to Spinal and Caudal Anesthesia: Relation to the Effect of Sympathectomy. II. Effect on Renal Circulation and Peripheral Resistance, Am. Heart J. **35**: 226, 1948.

CIRCULATORY RESPONSES TO SPINAL AND CAUDAL ANESTHESIA IN HYPERTENSION: RELATION TO THE EFFECT OF SYMPATHECTOMY

II. Effect on Renal Function

A. C. Corcoran, M.D., R. D. Taylor, M.D., and Irvine H. Page, M.D.*
Cleveland, Ohio

SPINAL anesthesia in normal subjects causes moderate arterial hypotension (average arterial pressure, 86 mm. Hg) with little change in the levels of renal blood flow and glomerular filtration rate.[1] An analysis of these data indicates that renal vascular resistance is decreased during the period of anesthesia and hypotension.[2] In contrast, the urea clearance of hypertensive subjects is often reduced during hypotension caused by high spinal anesthesia.[3] This change is the result of decreased renal blood flow and glomerular filtration.[4] These observations seem to suggest that there is an essential qualitative difference between the renal vascular responses of normotensive and hypertensive subjects.

However, we[5] have shown that the renal effects of high spinal anesthesia in patients suffering from essential hypertension are variable. In many, renal blood flow is increased and in most, glomerular filtration is depressed. The net renal change is expressive of renal vasodilation during the hypotension caused by spinal anesthesia. In other patients, there is either scant vasodilation or there appear varying degrees of renal ischemia.

We tentatively suggested that the response of the renal vasculature to high spinal anesthesia might be an index of the nature of the hypertensive process. Renal vasodilation after spinal anesthesia might then be taken as evidence of pre-existing increased vasomotor tone, and a failure of such vasodilation, as evidence of humoral vasoconstriction (as from activity of the renal pressor system) or of vascular rigidity due to renal arteriosclerosis. We went on to suggest that where the renal response indicated a predominance of vasomotor influence, sympathectomy should be helpful; and that where the renal vasoconstriction seemed to be due principally to renal pressor activity or vascular narrowing from sclerosis, sympathectomy would probably be unsuccessful.

From the Lilly Laboratory for Clinical Research, Indianapolis City Hospital, Indianapolis, Ind., and the Research Division of the Cleveland Clinic and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

Received for publication Aug. 14, 1947.

*Present address: Research Division, Cleveland Clinic Foundation, Cleveland, Ohio.

The present report is intended as a definitive presentation of the data concerning this hypothesis and includes observations on the renal functional effects of caudal anesthesia.

The major problems posed in the investigation are (1) the nature of the renal functional changes induced by high spinal and caudal anesthesia in patients with essential hypertension, and (2) the possibility of predicting in advance the results of sympathetic ganglionectomy from an analysis of these changes.

METHODS

1. *Spinal Anesthesia Group.*—These patients were under our observation in the clinic of the Lilly Laboratory for Clinical Research, Indianapolis City Hospital. One patient showed normal levels of arterial pressure; one, mild arterial hypertension (prehypertension); and seventeen, varying grades of essential hypertension, including one instance of the malignant syndrome.

Renal blood flow was estimated from Diodrast clearance and hematocrit index. Glomerular filtration rate was taken as equal to plasma inulin clearance. Hematocrit index, plasma protein content, and brachial arterial pressure were measured. These determinations were made one or two days before and again during spinal anesthesia. The measurements reported as control levels of renal blood flow and glomerular filtration are averages of matching calculations from three periods of urine collection and blood sampling. Urine collections were made by washing the bladder through a catheter with 150 c.c. of saline at ten- to fifteen-minute intervals. Results of such individual periods of urine collection during anesthesia are shown graphically in Fig. 2. The calculation of renal arteriolar resistances were made by the method of Lamport.[2] The values summarized in Tables I and III are averages usually of two or three such periods of collection after induction of anesthesia. The level of arterial pressure taken as the control is the average of three or more observations made during the control measurement of renal clearance, and the levels reported during anesthesia are averages of observations made at five-minute intervals. The arterial pressure recorded in all tables is the average of systolic and diastolic arterial pressures and thus approximates mean arterial pressure.

Ballistocardiograms were done in several patients by the method of Starr and Schroeder.[6] The calculations of cardiac index (cardiac output per minute per square meter of body surface) were made by correcting for variations of aortic size to ideal weight and surface area.

Anesthesia* was induced by intrathecal injection. Single injections were given three patients and fifteen were observed by the technique of continuous spinal anesthesia.

2. *Caudal Anesthesia Group.*—The patients studied† were selected from those under observation in the Research Division of the Cleveland Clinic or those recommended to the Section on Neurosurgery for lumbodorsal sympathectomy by the method of Smithwick.

---

*The anesthesia was under the supervision of Dr. Lillian Mueller, anesthesiologist, Indianapolis City Hospital, to whom we are most grateful for this assistance.

†We are indebted to Dr. W. James Gardner, who performed these operations, for the opportunity of studying patients under his care.

TABLE I. EFFECTS OF SPINAL ANESTHESIA

NO.	RBF C.C. PER MIN.		GFR C.C. PER MIN.		FF		R_A		R_E		R		Pm MM. HG		TIME		
	C	SP	C	SP	C	SP	C	SP	C	SP	C	SP	C	SP	LEVEL	MIN.	PERIOD
1	1459	1796	145	135	0.20	0.15	0.049	0.017	0.013	0.009	0.062	0.026	147	103	D6	15	1
2	1101	1070	118	95	0.19	0.15	0.055	0.021	0.016	0.014	0.071	0.035	132	93	D6	20	1-2
3	814	1049	120	109	0.23	0.16	0.059	0.034	0.031	0.018	0.090	0.052	135	115	D6	15	1
4	518	746	79	63	0.29	0.13	0.22	0.061	0.053	0.025	0.273	0.086	200	125	D6	12	3
5	1012	1241	96.5	107	0.18	0.17	0.061	0.0099	0.02	0.015	0.081	0.0247	140	90	D6	20	3-4
6	786	1280	82	96	0.18	0.13	0.079	0.016	0.022	0.011	0.101	0.027	133	87	L2	20	1-2
7	1143	1028	97	92	0.18	0.19	0.055	0.014	0.016	0.018	0.071	0.032	138	89	D6	12	5
8	691	975	76	73	0.19	0.13	0.13	0.037	0.027	0.015	0.157	0.052	170	106	D6	30	1-2-3
9	823	906	94	58	0.21	0.13	0.105	0.036	0.013	0.0056	0.118	0.0416	157	97	D5	30	1-2-3
10	581	772	80	44.7	0.26	0.10	0.083	0.027	0.048	0.023	0.131	0.050	138	96	D6	30	1-2-3
11	646	640	97.5	80.2	0.25	0.20	0.095	0.072	0.033	0.027	0.128	0.099	140	120	L1	20	1-2
12	952	1140	145	108	0.25	0.165	0.071	0.044	0.025	0.014	0.090	0.058	140	120	D7	32	1-2-3
13	801	854	103	127	0.24	0.25	0.077	0.055	0.024	0.024	0.101	0.079	138	122	D6	17	3-4
14	408	455	62	62	0.24	0.20	0.148	0.15	0.052	0.04	0.200	0.19	137	147	D9	20	1-2
15	1155	887	86	88	0.14	0.18	0.033	0.048	0.014	0.021	0.047	0.069	110	111	D9	40	1-2-3
16	882	1100	91	91	0.20	0.16	0.059	0.063	0.027	0.018	0.086	0.081	140	150	L2	30	1-2-3
17	618	607	71	83	0.19	0.22	0.062	0.044	0.026	0.03	0.088	0.074	108	95	D6	30	1-2-3

Control (*c*) and observations during anesthesia (*sp*). *RBF* = minimal renal blood flow calculated from plasma Diodrast clearance and hematocrit index. *GFR* = glomerular filtration rate from plasma inulin clearance. Both values are expressed as cubic centimeters per 1.73 square meters of body surface per minute. *FF* = filtration fraction. R_A = afferent resistance; R_E = efferent resistance. $R = R_A + R_E$, all calculated by the method of Lamport. *Pm* = average arterial pressure (mean of brachial systolic and diastolic pressures). *Level* indicates level of anesthesia as estimated from sensory loss. *Time* indicates the duration of the observations under anesthesia listed in the table, and *Period*, the number and approximate timing of the observations under anesthesia. Each period of urine collection extends over 10 to 20 minutes.

The order of the observations in this series was similar to that employed in the former group. It differed in that the clearance of para-aminohippurate was substituted for that of Diodrast in control observations. The analyses were done using a Coleman Model 6 Clinical Spectrophotometer.*

RESULTS

1. *Spinal Anesthesia Group.*—Data obtained from studies in the seventeen patients with essential hypertension are summarized in Table I. Observations on the one patient with minimal hypertension (prehypertension) are recorded in Fig. 2.

Effect on Blood Pressure of Anesthesia Level: Anesthesia reached the nipple line (D 5 to 6) in eleven, D 7 in one, D 9 in two, L 1 in one and L 2 in two patients. Arterial pressure was slightly increased in three patients with anesthetic levels of D 9 and L 2. Pressure was decreased by less than 20 mm. Hg in two patients with sensory loss at D 6, and by more than 20 mm. Hg to a range of from 85 to 125 mm. Hg in twelve whose levels of anesthesia reached from L 2 to D 5. Pressure was transiently decreased below 85 mm. Hg in two patients (Cases 7, 17 A) at sensory anesthetic levels of D 4 and D 5.

Effect on Renal Function: The course of renal function during anesthesia varied with the changes of arterial pressure encountered. No significant change of renal blood flow, glomerular filtration rate, or calculated renal arteriolar resistance occurred in patients whose arterial pressure was not altered or was slightly increased during anesthesia (Cases 14, 15, 16). Decreases of pressure of less than 20 mm. Hg did not alter renal blood flow or glomerular filtration rate in a consistant manner, but resulted in decreased afferent arteriolar resistance (Table I, Cases 13, 17). The effects of decreases of pressure of 20 mm. Hg or more to a range of from 85 to 125 mm. Hg are presented in Table I (Cases 1through 12) and summarized in Table II. The most frequent changes were increased renal blood flow, decreased glomerular filtration rate and filtration fraction, and decreased resistance of both afferent and efferent arterioles, as illustrated in Fig. 1. The pattern of response is exemplified in Fig. 2, Case 9. The mean average arterial pressure in this group during anesthesia was 103 mm. Hg and the mean decrease of pressure, 43 mm. of mercury.

These relationships of flow, filtration, and pressure are shown in detail for individual periods of urine collection for two patients whose arterial pressure decreased below 85 mm. of mercury. The one (Fig. 2, Case 17 A) showed an initial fall of pressure to 75 mm. Hg, with a decrease of about 30 per cent in renal blood flow and of more than 50 per cent in glomerular filtration rate. A further decrease of pressure to 68 mm. Hg exaggerated these changes. A transient increase of pressure to 100 mm. Hg increased glomerular filtration rate and caused a large gain beyond control levels in Diodrast clearance. As in other circum-

*We are indebted to Dr. Karl Beyer, Sharp & Dohme, Inc., for generous supplies of sodium p-aminohippurate and to Mr. E. D. Coleman, Coleman Instrument Co., for assistance in obtaining the use of a Model 6 Spectrophotometer.

TABLE II. CHANGES IN RENAL FUNCTIONS INDUCED BY SPINAL ANESTHESIA

NO.	RBF	GFR	FF	R_A	R_E	R	Δ Pm MM. HG	Pm SP. ANESTHESIA MM. HG
1	1.23	1.07	0.75	0.35	0.66	0.42	−44	103
2	0.97	0.81	0.79	0.39	0.91	0.50	−29	93
3	1.28	0.91	0.70	0.58	0.58	0.58	−20	115
4	1.44	0.80	0.45	0.30	0.47	0.34	−75	125
5	1.23	1.11	0.94	0.16	0.73	0.32	−50	90
6	1.63	1.17	0.72	0.20	0.50	0.27	−46	87
7	0.90	0.95	1.06	0.25	1.11	0.57	−49	89
8	1.41	0.96	0.68	0.27	0.57	0.32	−64	106
9	1.10	0.62	0.60	0.35	0.43	0.36	−60	97
10	1.33	0.56	0.38	0.32	0.42	0.36	−42	96
11	0.99	0.83	0.86	0.76	0.84	0.79	−20	120
12	1.19	0.74	0.67	0.61	0.33	0.56	−20	120
Mean	1.225	0.88	0.72	0.38	0.63	0.45	−43	103.4

The values of *RBF*, *GFR*, R_A, R_E, and *R* are the ratios of the observations during anesthesia to observations in control periods. The abbreviations have the same significance as in Table I. ΔPm is the difference between average arterial pressure during control periods and pressure during anesthesia.

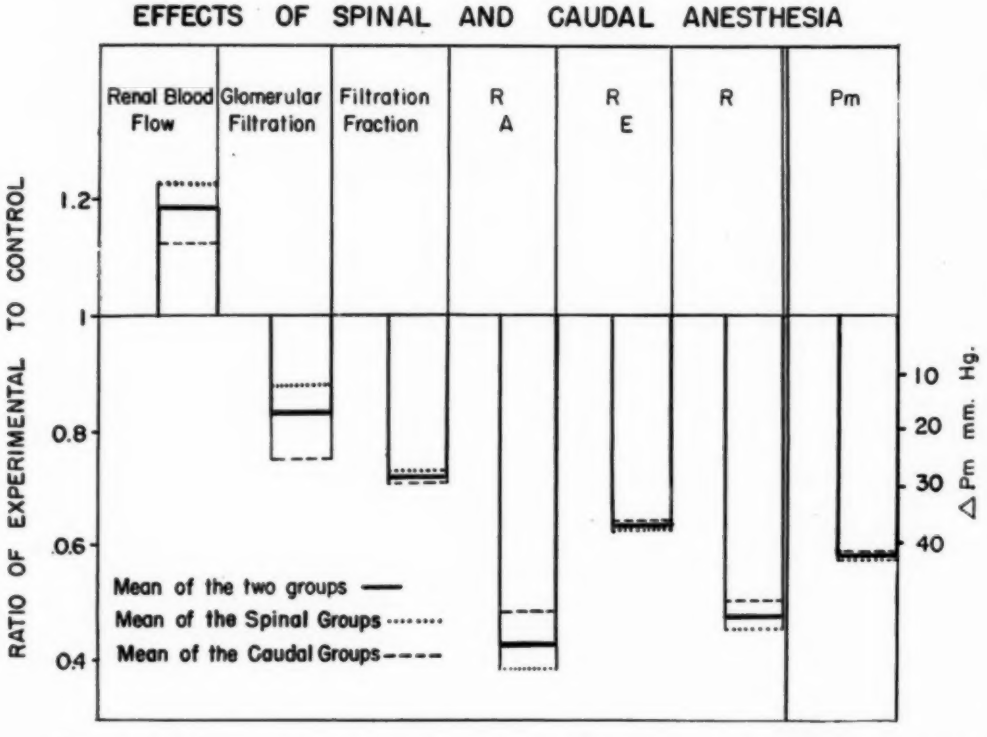

Fig. 1.—The changes in renal function consequent on spinal and caudal anesthesia and means of the changes during the two types of anesthesia. The values indicated are means from Tables II and IV. Changes in renal function are indicated as ratios of experimental observations to those during control. Mean changes in arterial pressure are indicated in mm. Hg from the mean control level.

stances in which hypotension causes partial cessation of glomerular filtration, this "overshoot" of Diodrast clearance is due to washing out, from the tubules, Diodrast secreted but not excreted during hypotension.[7] It is not, as it might seem, a compensatory hyperemia.

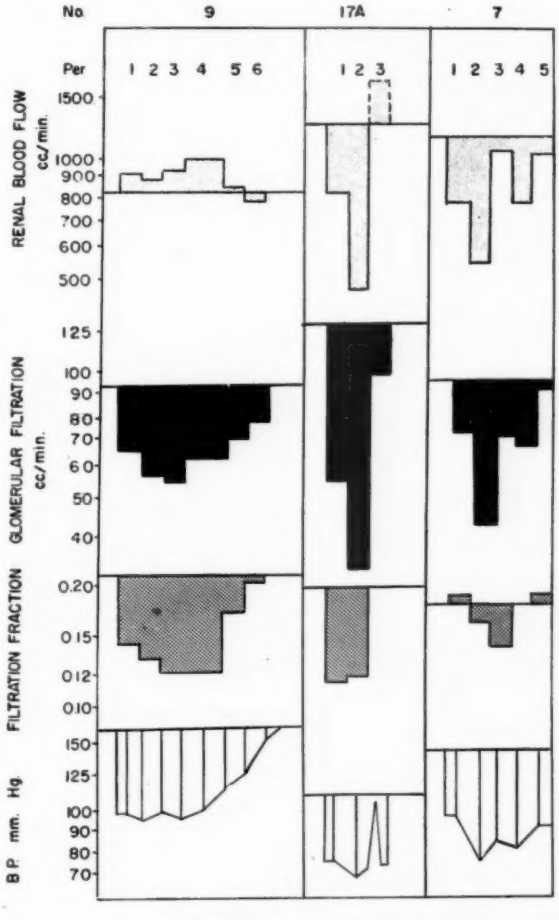

Fig. 2.—Changes in renal function induced by spinal anesthesia in three patients. *No.* = patient number. *Per.* = period of clearance determination under anesthesia, time being approximately ten minutes. The base line for each observation is the mean of control observations. *B.P.* = average arterial pressure in mm. of mercury. Observations on Case 9 are representative of the changes in the group of patients listed in Table II. Changes in Cases 17A and 7 are discussed in the text.

In the other patient (Fig. 2, Case 7), arterial pressure immediately after induction of spinal anesthesia was 95 mm. Hg average. In spite of this apparently satisfactory level of pressure, renal blood flow and glomerular filtration rate were decreased by about 30 per cent. A fall of pressure to 73 mm. Hg exaggerated these changes, but a subsequent rise of pressure to only 82 mm. Hg restored renal function to the levels which had obtained at 95 mm. of mercury. Flow and filtration again decreased when pressure fell to 78 mm. of mercury. Recovery of arterial

TABLE III. EFFECTS OF CAUDAL ANESTHESIA

NO.	RBF		GFR		FF		R_A		R_E		R		Pm		LEVEL	TIME (MIN.)	RESULT OF OPERATION	PERIOD
	C	CA	C	CA	C	CA	C	CA	C	CA	C	CA	C	CA				
18	1208	1012	141	53.5	0.22	0.10	0.0663	0.0422	0.0058	0.0020	0.072	0.046	139	96	D6	32	0	2
19	835	1050	146	93	0.31	0.15	0.057	0.029	0.024	0.0080	0.081	0.037	125	93	D6	25	0	2
20	1230	1228	86.6	100	0.15	0.13	0.052	0.035	0.004	0.005	0.056	0.039	125	105	D8	28	0	3
21	956	943	97.3	37	0.18	0.07	0.200	0.038	C.011	0.004	0.211	0.042	175	96	D5R	15	+	4
22	833	1174	97.4	108	0.21	0.16	0.066	0.029	0.018	0.009	0.084	0.038	132	105	D6	32	+	3
23	595	938	103	89	0.31	0.17	0.098	0.053	0.032	0.007	0.130	0.060	135	109	D5	36		3
24	829	835	78	113	0.15	0.22	0.086	0.049	0.013	0.020	0.099	0.069	141	118	D9	40	0	3
25	976	946	88.4	52	0.16	0.10	0.118	0.034	0.007	0.004	0.125	0.038	178	92	D6	24	+	3
26	796	980	152	183	0.32	0.25	0.117	0.074	0.025	0.014	0.142	0.088	169	140	L1	17	0	1
27	594	807	83	82	0.25	0.18	0.160	0.098	0.016	0.0074	0.176	0.105	155	135	L1	19	0	2
28	704	742	81	98	0.22	0.25	0.147	0.078	0.026	0.031	0.173	0.109	190	150	D9	34		2
29	767	793	79	82	0.20	0.20	0.156	0.100	0.019	0.018	0.175	0.118	200	160	D8	35	0	3
30	1121	799	106	102	0.17	0.23	0.054	0.054	0.010	0.023	0.014	0.077	135	126	L2	38		3
31	909	1004	111	101	0.22	0.19	0.134	0.089	0.015	0.011	0.149	0.100	198	153	L2	34		3
32	638	497	86	65	0.28	0.27	0.182	0.169	0.016	0.02	0.198	0.189	182	149	L3	41	+	3
33	528	754	90	85	0.27	0.18	0.172	0.113	0.026	0.011	0.198	0.124	155	143	D7	13	+	1
34	953	443	80	34	0.17	0.13	0.129	0.182	0.007	0.012	C.136	0.194	180	129	D6	32	0	3
35	834	385	118	29	0.22	0.12	0.1032	0.085	0.012	0.015	0.1156	0.099	145	82	D4		0	

The abbreviations have the same significance as in Table I. Observations under caudal anesthesia are indicated as *CA*. The control observations of *RBF* were made from the plasma clearance of p-aminohippurate and the hematocrit index.

pressure to 88 mm. Hg all but restored these functions to the control levels. Similar initial decrease of blood flow and glomerular filtration at levels of arterial pressure greater than 85 mm. Hg were observed in two other patients (Cases 4 and 5) and were also followed by restoration of these functions to or above control rates at levels of pressure lower than those associated with renal ischemia at the onset of anesthesia.

2. *Caudal Anesthesia Group.*—The eighteen patients studied in this series include one with very mild essential hypertension. The average severity of the disease in this group was greater than in that studied under spinal anesthesia. Most of these patients underwent bilateral lumbodorsal sympathectomy and ganglionectomy. Observations on these patients are listed in Table III.

Effect on Blood Pressure; *Level of Anesthesia*: Arterial pressure was decreased by less than 20 mm. Hg in two patients whose sensory levels of anesthesia were L 2 and D 7 (Cases 30 and 33). Decreases of 20 mm. Hg or more, but to average levels greater than 125 mm. Hg, occurred in five patients at sensoryanesthetic levels of D 6, D 8, D 9, L 1, L 2, and L 3. In eight patients the drop of arterial pressure was of 20 mm. Hg or more and the levels reached ranged between 85 and 125 mm. Hg (Cases 18 through 25). Sensory anesthetic levels in this group ranged from D 5 to D 9. In one patient (Case 35) the average pressure was less than 85 mm. Hg at a sensory level of D 4.

Effect on Renal Function: No definite changes of renal function were observed in the two patients whose pressure decreased less than 20 mm. of mercury. In the group whose pressures fell by 20 mm. Hg or more to levels greater than 125 mm. Hg, three showed an increase of renal blood flow; two, no change; and one, a definite renal ischemia. Glomerular filtration was increased in two, unchanged in two, and decreased in two subjects. The decrease in glomerular filtration occurring in the patient who showed renal ischemia during the drop in pressure was of the order of 40 per cent.

As in the former series, we are most concerned with the changes of function encountered in patients whose pressures fell by 20 mm. Hg or more to levels of between 85 and 125 mm. Hg average arterial pressure. Comparative preanesthetic and postanesthetic data from these are summarized in Table IV. The averages of

TABLE IV. CHANGES IN FUNCTIONS INDUCED BY CAUDAL ANESTHESIA

NO.	RBF	GFR	FF	R_A	R_E	R	Δ Pm MM. HG	Pm CAUDAL
18	0.84	0.38	0.43	0.64	0.34	0.64	−43	96
19	1.25	0.66	0.48	0.51	0.33	0.45	−32	93
20	1.00	1.15	1.15	0.67	1.26	0.71	−20	105
21	0.98	0.38	0.39	0.19	0.36	0.20	−79	96
22	1.41	0.83	0.76	0.44	0.49	0.45	−27	105
23	1.58	1.10	0.55	0.54	0.22	0.46	−26	109
24	1.01	0.92	1.43	0.57	1.54	0.70	−23	111
25	0.97	0.59	0.63	0.29	0.57	0.30	−86	92
Mean	1.13	0.75	0.73	0.48	0.64	0.50	−42	100

The abbreviations have the same significance as in Table II.

the changes in the group are increased renal blood flow and decreased glomerular filtration. The comparative means of the responses are graphically presented in Fig. 1 where the data from caudal and spinal anesthetic groups are compared and averaged.

With caudal anesthesia, as with spinal anesthesia, decrease of arterial pressure to levels less than 85 mm. Hg resulted in renal ischemia (Case 35). One patient (Case 21) showed renal ischemia and oliguria at pressures of 87 and 81 mm. Hg, which were followed by a return to normal function at 96 mm. of mercury. Two patients (Cases 32 and 34) showed renal ischemia and decreased glomerular filtration at levels of pressure greater than 125 mm. of mercury.

3. *Effect of Spinal Anesthesia on Peripheral Resistance.*—The effects of spinal anesthesia on blood pressure, pulse rate, cardiac output, and peripheral resistance are summarized in Table V. Pulse rate was decreased during anesthesia.

TABLE V. EFFECT OF SPINAL ANESTHESIA ON BLOOD PRESSURE, PULSE RATE, AND CARDIAC OUTPUT

NO.	PERIOD	Pm MM. HG	PULSE (PER MIN.)	CARDIAC INDEX L. PER MIN. PER SQ. M.	P.R. (PER CENT)
5	Control	140	76	2.15	100
	1	115	66	1.74	101
	2	90	66	1.79	76
	3	83	60	1.80	70
8	Control	157	72	1.46	100
	1	125	66	1.2	96
	2	110	60	1.2	85
	3	100	62	1.2	77
36	Control	107	70	1.86	100
	1	75	80	2.13	61
	2	68	60	1.76	67
	3	73	60	1.94	65
13	Control	138	96	1.6	100
	1	135	92	1.7	100
	2	125	84	1.94	81
	3	121	72	1.71	89
	4	117	78	2.00	74
	5	106	78	1.8	74
14	Control	171	69	1.79	100
	1	145	60	1.98	76
	2	147	60	1.96	79
	3	145	60	1.97	76
	4	147	60	1.97	78
15	Control	107	70	1.86	100
	1	75	80	2.13	61
	2	68	60	1.76	66
	3	73	60	1.94	65

No. indicates the number given the patient. *Pm* has the same significance as in other tables. *C.I.* indicates the cardiac index (cardiac output per square meter of body surface) as estimated from the ballistocardiogram. *P.R.* indicates peripheral resistance, calculated from cardiac index and average arterial pressure. The level found in control periods is taken as 100 and levels in succeeding observations under spinal anesthesia are expressed as per cent of the control.

The decrease of arterial pressure after induction of anesthesia was initially associated with decreased cardiac output in three patients. But in later periods of observation in these, and from the outset in the others, peripheral resistance was decreased during anesthesia.

4. *Prediction of Effect of Sympathectomy.*—The evaluation of results of lumbodorsal sympathectomy and ganglionectomy is made in the manner described in the preceding paper.[8] The data are presented in Table III. There is no positive correlation of renal functional changes under caudal anesthesia with the end result of operation. The prediction from renal changes may aid in excluding patients, since results of operation were unsatisfactory in two patients who showed decreased renal blood flow during anesthesia.

DISCUSSION

The effects of spinal and caudal anesthesia are similar. Hence, they are discussed together.

Anesthetic Level and Arterial Pressure.—The degree of change in arterial pressure during anesthesia is not directly related to the level of sensory anesthesia. However, lower levels of sensory loss are usually associated with lesser falls of pressure, and the highest levels of anesthesia (D 4 and 5) are associated with the lowest levels of pressure.

Renal Function.—In every instance in which anesthesia decreased arterial pressure, it induced renal vasodilation, as shown by a decrease in renal resistance (*R*). The net effect of anesthesia on renal blood flow and function depends on the balance struck between the change in pressure and the change in resistance.

The results in patients whose arterial pressures were significantly decreased (20 mm. Hg or more) to levels ranging about the normal (85 to 125 mm. Hg average pressure) are of special clinical and physiologic interest. These are the levels of arterial pressure reached after successful surgical treatment of hypertension. Further, they represent an abrupt transition from the hypertensive to the normotensive state. The means in this group reveal increased renal blood flow, decreased glomerular filtration rate, and decreased resistance to the flow of blood through the renal arterioles (Tables II and IV). The fact that renal blood flow increases in this group by about 20 per cent during a reduction of arterial pressure which averages 43 mm. Hg is evidence of a positive balance between pressure and resistance. From this it follows that resistance has decreased more than arterial pressure.

Glomerular filtration depends upon the maintenance of a relatively high intraglomerular hydrostatic pressure. It is, therefore, not surprising that glomerular filtration rate is somewhat decreased during the fall in pressure in this group of patients. In normal subjects, glomerular filtration rate is decreased by about 10 per cent during spinal anesthesia which reduces arterial pressure to 89 mm. of mercury.[1] In our patients it is reduced about 17 per cent during a drop in pressure to 103 mm. of mercury. The depression of filtration rate in the hypertensive group

is by no means great enough to jeopardize renal excretory function. However, the decrease in filtration appears in these patients at a mean average arterial pressure of 103 mm. Hg rather than 89 mm. Hg, and averages 17 rather than 10 per cent. This suggests that in the hypertensive patient there is some factor which prevents all the normal gradient of arterial pressure from reaching the glomerular capillaries. The most probable factor is a residual increased afferent arteriolar resistance, not abolished by spinal or caudal anesthesia. The decreases in afferent and efferent arteriolar resistances which occur during anesthesia indicate that anesthesia results in vasodilation consequent on denervation. The abnormal residue of afferent resistance which tends to interfere with glomerular filtration under anesthesia in hypertensive patients may be construed as a vasoconstriction of humoral origin such as might result from the activity of the renal pressor system or as an inability of the afferent arterioles to dilate consequent to arteriolosclerosis.

The significant conclusions from the data obtained in this group of patients are that there is no essential qualitative abnormality in the renal vascular responses of hypertensive patients to spinal or caudal anesthesia, and that the changes which do appear are principally the result of renal vasodilation.

Our data would seem at first glance to contradict those of Gregory and coworkers,[4] who observed decreased rather than increased renal blood flow during hypotension due to spinal anesthesia in hypertensive patients. The contradiction is largely due to the choice of different experimental methods. These observers carried the level of anesthesia to D 2 or higher, thus obtaining lower levels of arterial pressure during anesthesia than prevailed in most of our observations. Intervals of collection extended over one hour in their experiments, whereas in ours the changes in renal circulation were measured at frequent intervals. However, we are unable to explain their failure to observe a rather consistent decrease of filtration fraction during hypotension.

Certain of our observations agree very well with those of these workers. Thus, at levels of average pressure less than 85 mm. Hg, we found depression of renal blood flow and glomerular filtration. Similar changes appear during hypotension in normal subjects.[1] Their presence is not evidence of a specific hypertensive abnormality. Our data also agree in that two patients showed decreased renal blood flow and filtration rate at pressure levels greater than 125 mm. of mercury. The cause of the failure of renal vasodilation in these patients is not apparent. It may be that the effect of anesthesia was inadequate or that the renal arterioles in these patients were so diseased as to be incapable of vasodilation. The tendency in certain patients for blood flow and glomerular filtration to decrease during the drop of pressure immediately after induction of anesthesia and then to return to control levels or above as anesthesia and hypotension continue is of particular interest. As we have seen, most hypertensive patients respond to anesthesia and hypotension by renal vasodilation, from which it may be concluded that the normal capacity of the renal vessels to adapt to changing levels of arterial pressure is maintained. In two patients this capacity seemed to be lost. It seemed to be slowed in the patients showing a biphasic response of blood flow resistance and blood pressure. The biphasic pattern of change in renal resistance

was paralleled in three patients by the changes of peripheral vascular resistance (Table V). This was unchanged immediately after anesthesia and later fell as hypotension persisted. The mechanism of this adaptative sequence is a matter of speculation.

In summary, spinal and caudal anesthesia induce, in most patients with hypertension, decrease in arterial pressure, increase in renal blood flow, and a slight decrease in glomerular filtration. The sequence of these renal changes is only consistent with renal arteriolar vasodilation. In a few patients this renal response is deficient or slowed.

Mechanism of Vascular Responses.—The cause of the changes in renal and systemic vascular resistance must now be examined. Does the decrease in resistance result from decreased cardiac output and arterial pressure, or as seems more likely, does the decrease of pressure result from decreased peripheral resistance, in which renal resistance is a large component? Smith and co-workers[1] suggested that the hemodynamic changes caused by spinal anesthesia in normal subjects reflect decreased venous return, with consequent decreased stroke volume and cardiac output and a resultant decrease of arterial pressure. They attributed the decrease in venous return to postarteriolar (capillaries, venules, veins) dilatation due to widespread paralysis of skeletal muscle. Widespread muscle paralysis does not occur in the course of caudal anesthesia. The renal and systemic vascular responses to spinal and caudal anesthesia are very similar, if not identical. We must conclude, therefore, that postarteriolar dilatation with decreased venous return due to muscle paralysis is not the principal factor in the hemodynamic changes induced by either spinal or caudal anesthesia.

This conclusion is confirmed by our observations on the effect of spinal anesthesia on cardiac output and peripheral resistance. Three patients showed decreased output and arterial pressure with unchanged peripheral resistance at the outset of anesthesia. This sequence is consistent with decreased venous return and cardiac output as the major factor in lowering blood pressure. Later in these observations, however, and throughout the others, the principal element in the decrease of arterial pressure is decreased peripheral resistance. To the extent that cardiac output remains slightly depressed in some of these observations, it may be that venous return is slowed by skeletal muscle paralysis. But the large decreases in both peripheral and renal resistances speak for actual arterial and arteriolar dilatation. Unfortunately, no data on cardiac output are available for the caudal anesthesia group. If our view is correct, caudal anesthesia should differ from spinal anesthesia in that the decrease of arterial pressure would be entirely, rather than only principally, due to decreased peripheral resistance.

Thus, the mechanism of the renal and systemic vascular changes accompanying spinal and caudal anesthesia seems to be principally arteriolar vasodilation, although venous pooling with decreased venous return may contribute to the tendency to decreased cardiac output in patients submitted to spinal anesthesia.

Vasodilation is thus seen to be a major factor in the decrease of arterial pressure, and since it is elicited by a procedure which temporarily paralyzes spinal outflow, it must be concluded that it is due to interruption of nerve im-

pulses. In normal subjects, such vasodilation results only in maintenance of normal rates of renal blood flow at slightly decreased arterial pressures, and reflects the autonomy of the renal circulation, that is, the capacity to maintain normal rates of blood flow during wide fluctuation of pressure. In hypertensive subjects the vasodilation is commonly followed by an actual increase in renal blood flow in the face of considerable decreases of arterial pressure. We must conclude that the renal vessels of hypertensive patients are under abnormal stimulation to an extent that denervation often results in vasodilation and increased renal blood flow at approximately normal levels of arterial pressure. So large a fraction of the cardiac output traverses the renal circulation that a considerable proportion of the decrease in peripheral resistance observed in some hypertensive patients is contributed by renal vasodilation. But we confirm the view of Gregory and Levin[9] that increased renal blood flow is not the cause of the decrease in arterial pressure during high spinal anesthesia.

The mechanism by which high spinal and caudal anesthesia lead to vasodilation of arterioles, including those of the kidney, is unknown. Our unpublished observations on the effect of these procedures in dogs with experimental renal hypertension due to perinephritis show an exact similarity with the renal functional changes found in hypertensive patients. These procedures do not, therefore, reveal a difference in mechanism between experimental hypertension of known renal origin and the essential hypertension of human patients, as we had once thought they might. Both types of anesthesia cause a functional denervation which we assumed to be equivalent to that of lumbodorsal sympathectomy with ganglionectomy. But this operation does not increase renal blood flow in hypertensive patients, nor does it decrease arterial pressure in renal hypertensive dogs. It is possible that the vasodilation caused by high spinal and caudal anesthesia is due to a denervation other than that which is effected by lumbodorsal sympathectomy and ganglionectomy, or that the differences between the responses to operation and to anesthesia reflect the difference in the duration of the two procedures. Again, it may represent a change in the vasoconstrictor-vasodilator balance of vascular responsiveness of the order similar to that observed after injection of tetraethyl ammonium or destruction of the spinal cord.[10]

Our observations are entirely inconsistent with the view that essential hypertension is a compensation for increased renal vascular resistance, whether due to arteriosclerosis or other causes. True, a decrease of arterial pressure to very low levels depresses renal blood flow in hypertensive patients. But the same is true in normal subjects. In a few patients renal blood flow falls below control levels at levels of arterial pressure which are normal or above the normal, and it may be that in these the disease has advanced to the point where the vessels can no longer adjust to normal levels of arterial pressure. These instances, however, are exceptional in this group. The slight decrease in glomerular filtration which may occur during spinal and caudal anesthesia, even in subjects whose renal blood flow has been increased, suggests a presence of a small degree of fixed abnormal afferent arteriolar resistance. Clinically, this residue is insignificant and cannot serve as a contraindication to procedures which decrease arterial pressure.

Prediction of Effect of Sympathectomy.—Our hope of predicting the end result of lumbodorsal sympathectomy and ganglionectomy was not realized. This fact supports the view that the hemodynamic effects of sympathectomy differ significantly from those occurring during spinal or caudal anesthesia.

CONCLUSIONS

1. High spinal or caudal anesthesia which reduces average arterial pressure in hypertensive patients by 20 mm. Hg to levels ranging from 85 to 125 mm. Hg usually causes renal vasodilation, resulting in increased renal blood flow and a slight decrease in glomerular filtration rate. The observations are inconsistent with the view that essential hypertension is a compensation for increased renal vascular resistance.

2. Qualitatively, the renal vascular responses of normotensive and hypertensive patients to these procedures are identical. Quantitatively, they may differ slightly in that, in hypertension, a fraction of afferent arteriolar resistance is not removed by anesthesia.

3. The renal vasodilator response to anesthesia in hypertension indicates that a large proportion of increased renal vascular resistance in this disease is dependent on nervous influences which are affected by anesthesia extending to about D 5, or that denervation by anesthesia has sensitized vasodilator influences.

4. The major hemodynamic change induced by spinal or caudal anesthesia is seen to be due to decreased peripheral resistance.

5. Exceptionally, a few hypertensive patients show deficient or slowed renal vasodilator responses to spinal or caudal anesthesia. Two such patients failed to benefit from lumbodorsal sympathetic ganglionectomy. But operation was equally ineffective in patients whose responses were vasodilator. The renal vascular response to anesthesia is not a positive guide in the selection of patients, although the absence of vasodilation during anesthesia may contraindicate operation.

REFERENCES

1. Smith, H. W., Rovenstine, E. A., Goldring, W., Chasis, H., and Ranges, H. A.: The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man With Reference to the Autonomy of the Arterioles, and Especially Those of the Renal Circulation, J. Clin. Investigation **18**:319, 1939.
2. Lamport, H.: Formulae for Afferent and Efferent Arteriolar Resistance in the Human Kidney: an Application to the Effects of Spinal Anesthesia, J. Clin. Investigation **20**:535, 1941.
3. Gregory, R., Lindley, E. L., and Levine, H.: Studies on Hypertension. I. The Effect on the Renal Function of Decreasing the Blood Pressure of Patients With Hypertension, Texas Rep. Biol. and Med. **1**:59, 1943.
4. Gregory, R., Levin, W. C., Ross, G. T., and Bennett, A.: Studies on Hypertension. VI. Effect of Lowering the Blood Pressures of Hypertensive Patients by High Spinal Anesthesia on the Renal Function as Measured by Inulin and Diodrast Clearances, Arch. Int. Med. **77**:385, 1946.
5. Page, I. H., Taylor, R. D., Corcoran, A. C., and Mueller, L.: Correlation of Clinical Types With Renal Function in Arterial Hypertension. II. Effects of Spinal Anesthesia, (Proc. Cent. Soc. Clin. Res.) J. A. M. A. **124**:736, 1944.
6. Starr, G., and Shroeder, H.: Ballistocardiogram. II. Normal Standards, Abnormalities Commonly Found in Diseases of the Heart and Circulation, and Their Significance, J. Clin. Investigation **19**:437, 1940.

7. Corcoran, A. C., and Page, I. H.: Effects of Hypotension Due to Hemorrhage and of Blood Transfusion on Renal Function in Dogs, J. Exper. Med. **78**:205, 1943.

8. Taylor, R. D., Birchall, R., Corcoran, A. C., and Page, I. H.: Circulatory Responses to Spinal and Caudal Anesthesia in Hypertension: Relation to the Effect of Sympathectomy. I. Effect on Arterial Pressure, AM. HEART J. **35**:221, 1948.

9. Gregory, R., and Levin, W. C.: Studies on Hypertension; Effect of High Spinal Anesthesia on Blood Pressure of Patients With Hypertension and Far-Advanced Renal Disease—Its Possible Relationship to Pathogenesis of Hypertension, J. Lab. & Clin. Med. **30**:1037, 1945.

10. Page, I. H., and Taylor, R. D.: Mechanism of Renin Tachyphylaxis: Restoration of Responsiveness by Tetraethyl Ammonium Ion, Science **105**:622, 1947.

EXPERIMENTAL STUDIES ON AURICULAR FLUTTER AND AURICULAR FIBRILLATION

D. Scherf, M.D., New York, N. Y., F. J. Romano, M.D., Buenos Aires, Argentina, and R. Terranova, M.D., New York, N. Y.

IT IS possible to produce an auricular tachycardia of approximately 200 to 300 beats per minute by the injection of 0.05 c.c. of a 0.05 per cent solution of aconitine into the walls of the auricles.[31] In the experiments in which this observation was made the site of the injection was the left or right auricular appendix. The tachycardia appeared within one or two minutes and lasted as long as sixty minutes. Faradic stimulation of the vagus nerves in the neck during the presence of this tachycardia provoked a remarkable acceleration of the rate in all experiments. In some instances this increase in rate exceeded 100 per cent. Isolation of the injected auricular appendix from the rest of the heart by a clamp immediately ended the tachycardia. Upon removal of the clamp the tachycardia reappeared within a few seconds. Cooling of the site of injection immediately abolished the tachycardia. It recurred quickly and invariably whenever the cooling thermode was removed.[31]

In the earlier experiments it could not be decided whether the tachycardia was auricular flutter or whether it was an "essential" paroxysmal tachycardia. In these experiments vagal stimulation never terminated the tachycardia nor was auricular fibrillation or the phenomenon of re-excitation observed to follow this maneuver. Repeated reference has been made to the difficulties encountered in differentiating between auricular flutter and paroxysmal auricular tachycardia, and the possible identity of these conditions has been discussed.[3, 5, 9]

If a circus movement causes the tachycardia which follows the injection of aconitine, the result of cooling is unusual. One would be forced to assume that the circus wave is always located at the site of the injection in the auricular appendices. While it is conceivable that a circus movement ceases when the path of the circulating wave is cooled, it is difficult to explain how the circus movement always recurs immediately when cooling is interrupted. The increase of rate during vagus stimulation is, according to the circus movement theory, readily explained. The shortening of the refractory phase causes islands of refractory tissue to disappear and makes the central wave move faster on its shortened path.

If it is assumed, however, that the mechanism underlying the tachycardia is a rapid stimulus formation in a center rather than a circus movement, then

From the Department of Medicine, the New York Medical College.
Received for publication May 28, 1947.

the increase of rate during the vagus stimulation is an unusual phenomenon which requires explanation. The effect of the cooling is readily understandable.

In order to shed more light on the problems involved, experiments were resumed, with one important modification. The aconitine was injected in the area of the head of the sinus node, near the angle between the superior vena cava and the right auricular appendix. In this way, it was hoped that the response of specific tissue to the focal administration of aconitine could be determined.

METHOD

The hearts of dogs were exposed in the usual manner during Nembutal anesthesia. Artificial respiration was instituted. The vagus nerves were cut in the neck. The electrocardiogram was invariably taken on Lead II. The solution of aconitine was prepared in the same concentration that was used in previous experiments (0.05 per cent); since it deteriorates rapidly, no solution older than four weeks was used. As has been stated, 0.05 c.c. of the solution was injected near the head of the sinus node into the taenia terminalis. The presence of additional subepicardial connective tissue and of a greater muscle mass at this site usually prevents direct injection into the blood stream; this accident often precipitates ventricular fibrillation immediately. Only three of twenty-one experiments were marred by the development of ventricular fibrillation soon after the injection.

RESULTS

Auricular Fibrillation and Cooling of the Focus of Injection.—The injection of the aconitine solution around the sinus node was invariably followed by the sudden onset of a regular tachycardia with the same average rate and other characteristics that were observed in the tachycardia resulting from injection into the appendices.[21] The P waves were always high and positive in Lead II and the rate was extremely regular. An important difference, however, was the frequent appearance of auricular fibrillation, which was observed in fifteen experiments. In twelve experiments auricular fibrillation appeared spontaneously and three times it was observed during or shortly after faradic stimulation of a vagus nerve. Occasionally, it lasted only a few seconds or minutes, but in nine experiments it persisted for the duration of the experiment unless it was abolished by certain measures which will be discussed presently.

In the first portion of the tracing shown in Fig. 1, there is a regular auricular tachycardia with a rate of 352 per minute. There is a 2:1 A-V block. Faradic stimulation of the right vagus immediately led to auricular fibrillation (middle of the tracing) with an auricular rate of approximately 1,500 impulses per minute. The beginning and end of the brief vagus stimulation are clearly visible because the induction current deforms the tracing slightly.

The change from the regular auricular tachycardia to fibrillation, and vice versa, often occurred independently of vagus stimulation. Thus, in Fig. 2,*A*, a regular auricular tachycardia with a rate of 370 changes into auricular fibrillation shortly after faradic stimulation of the right accelerans nerve; the tracings shown

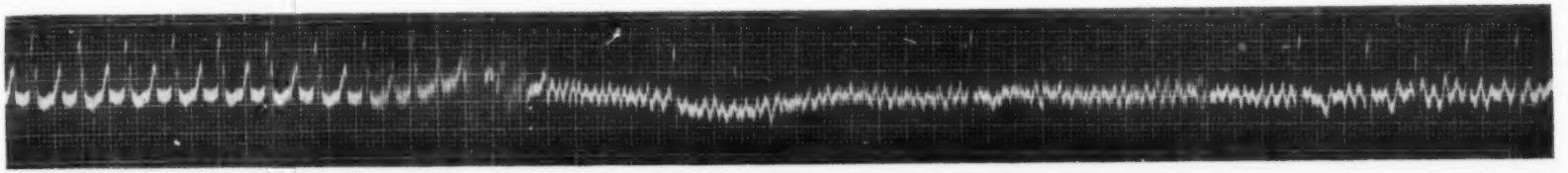

Fig. 1.—Faradic vagus stimulation changes auricular flutter into fibrillation.

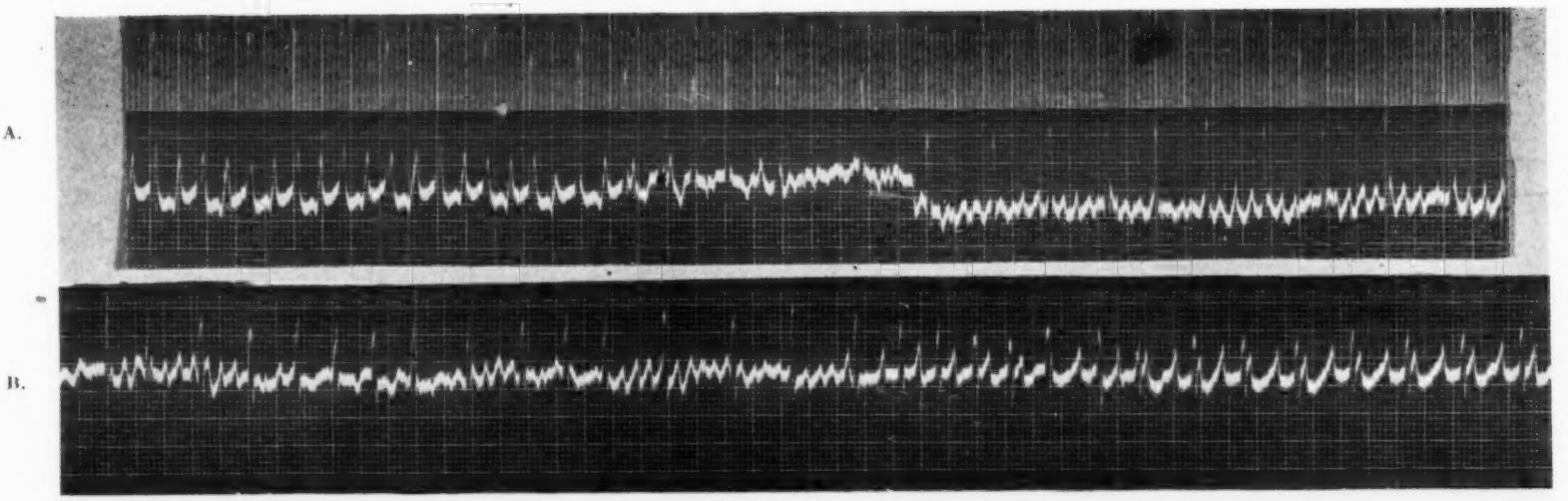

Fig. 2.—*A* shows the change from flutter into fibrillation; in *B*, fibrillation changes into flutter.

in Fig. 2,*B*, were obtained in another experiment, and auricular fibrillation, which had appeared soon after stimulation of the right accelerans nerve, changes into a regular auricular tachycardia with a rate of 300 per minute.

Cooling of the injected area in the region of the head of the sinus node was attempted in those experiments in which fibrillation, either induced by vagus stimulation or arising spontaneously, persisted for any length of time. The site of injection was clearly visible as a small gray blister with a diameter of 2.0 to 3.0 mm.; it was formed by the separation of the epicardium from the underlying tissue. In nine experiments, the cooling with a thermode promptly abolished the auricular fibrillation and led to sinus rhythm. Cessation of the cooling caused the immediate reappearance of the fibrillation. If the cooling was continued for more than two or three seconds, then at the end of the cooling the regular tachycardia appeared first and was soon followed by auricular fibrillation. This effect of cooling was obtained repeatedly (up to four times) during the same experiment.

Fig. 3 shows two tracings which demonstrate the effect of cooling. The top tracing shows auricular fibrillation which appeared after the injection of aconitine and persisted throughout the experiment. Cooling immediately abolished the fibrillation and two normal sinus beats are seen. The second sinus beat is again followed by fibrillation, since the thermode was immediately removed when the fibrillation ceased. The interval between the first abolition of fibrillation and its reappearance in Fig. 3,*A*, is seen to be less than 2.5 seconds. In the second tracing (Fig. 3,*B*), recorded in another experiment, persistent auricular fibrillation also followed the injection of aconitine in the area of the head of the sinus node. In this instance the cooling was applied for a longer time. Cooling immediately produced sinus rhythm. After the cooling, the thermode was removed and a regular tachycardia can be seen to follow. At the sixteenth beat this again changes into fibrillation. The interval between the end of the fibrillation and the reappearance of the tachycardia measures approximately 6.8 seconds. The appearance of a regular auricular tachycardia after the fibrillation had been stopped by cooling and its quick and spontaneous change into auricular fibrillation was repeatedly seen in several experiments.

Only when auricular fibrillation followed the accidental injection of a minute amount of the aconitine into the blood stream, or when the aconitine was spilled over a larger area of the right auricle, or when late in the experiment the aconitine spread by diffusion over the auricular muscle did cooling of the site of injection fail to bring the auricular fibrillation to a sudden end.

In eleven experiments a regular auricular tachycardia followed the injection of aconitine. As will be pointed out, we consider this regular tachycardia to be auricular flutter. Cooling of the injected area invariably and immediately abolished this tachycardia, which returned within one to two seconds after the cooling was interrupted. Table I shows the auricular rates before and after cooling. It is evident from the table that the rate immediately after the return of the tachycardia was, with rare exceptions, the same as the rate before the cooling.

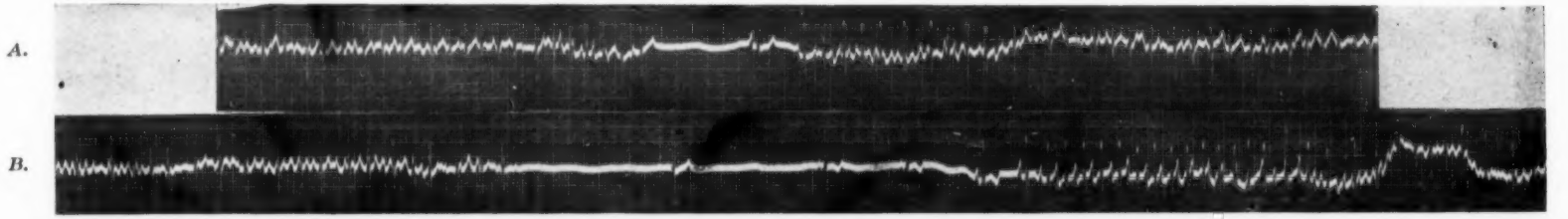

Fig. 3.—In *A*, auricular fibrillation is stopped by cooling the focus of injection of aconitine; removal of the thermode caused the fibrillation to reappear. In *B*, the cooling was continued for a longer time. After interruption of the cooling, flutter appears and is soon followed again by fibrillation.

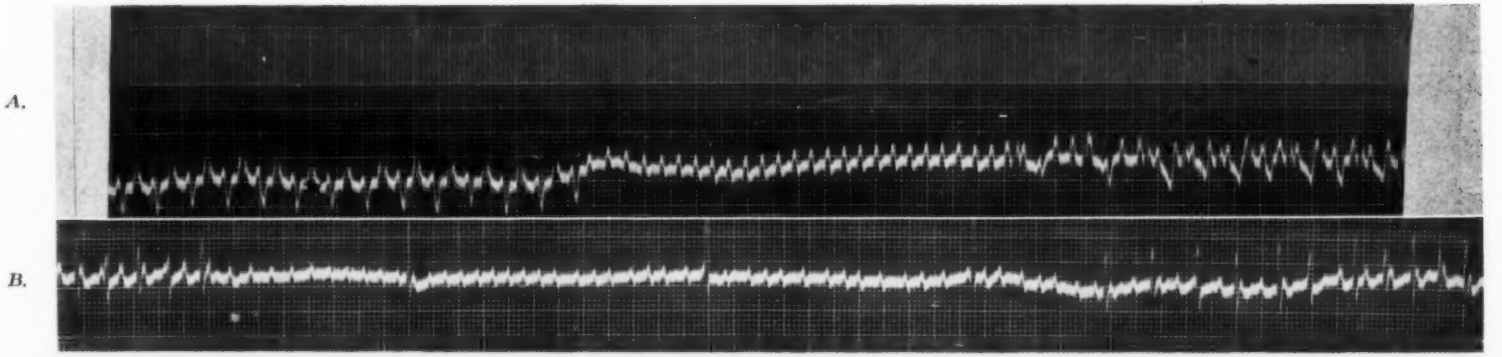

Fig. 4.—*A* shows, at the beginning, auricular flutter with 2:1 A-V block. During vagus stimulation the rate of the auricle increased slightly. In *B* vagus stimulation was accompanied by a considerable increase of auricular rate.

TABLE I. AURICULAR RATE BEFORE AND AFTER COOLING

DATE	BEFORE	AFTER
12/31	33[illegible]	330
	300	300
1/24	230	230
	248	248
2/4	248	248
	214	214
	272	272
	240	240
2/18	272	272
2/26	352	352
	272	272
3/4	248	230
	230	240
	330	330
	230	230
3/18	214	230
	6[illegible]	300
3/25	375	375
4/1	300	300
	426	426
	330	330
4/8	290	272
4/29	390	390

Vagus Stimulation During the Regular Tachycardia.—Whenever the solution of aconitine was injected into the auricular appendices, vagal stimulation caused a remarkable increase of the rate of the auricles.[31] After an injection of aconitine into the region of the head of the sinus node, faradic stimulation of the right or left, or both, vagus nerves failed to increase the rate in three out of thirteen experiments. In most of the other experiments the rate increased only moderately, even when both vagus nerves were stimulated simultaneously. In some instances the rate underwent a considerable increase whenever vagus stimulation was tried. Table II shows the rates of the auricle before, during, and immediately after vagus stimulation in all instances in which it was tried. In all experiments in which vagus stimulation increased the auricular rate, the rapid return of the rate to its former level as soon as the stimulation was discontinued was clearly evident.

In Fig. 4,*A*, (date of experiment indicated in Table II as 1/7), the auricular rate is 428 and the ventricular rate is 214 per minute, with the blocked P waves hidden in the QRS complex. During faradic stimulation of the right vagus nerve in the neck, the 2:1 A-V block disappeared and a complete A-V block developed. The auricular rate increases to approximately 461 per minute. After the vagus stimulation was stopped, the disturbance of the A-V conduction persisted for some time but the picture which existed before the stimulation soon reappeared.

The tracing shown in Fig. 4,*B*, (date of experiment indicated in Table II as 3/18) was obtained in another experiment. A regular auricular tachycardia with a rate of 280 per minute and partial A-V block are seen. Faradic stimulation of the right vagus in the neck again inhibited A-V conduction completely and simul-

taneously increased the auricular rate up to 500 per minute. A slight auricular arrhythmia, with group formation of three auricular beats followed by a longer diastole, is visible. With interruption of the vagus stimulation the initial picture reappeared quickly. This is one of the rare instances in which the form of the P waves changed during vagus stimulation.

TABLE II. AURICULAR RATE BEFORE, DURING, AND AFTER VAGUS STIMULATION

DATE	BEFORE	DURING	AFTER
11/26	300	330	300
	428	461	426
	352	375	352
12/17	214	230	214
	248	262	248
	290	316	290
12/31	248	260	248
1/7	214	230	214
	428	500	428
2/4	248	285	248
	272	300	300
	230	248	187
2/11	374	374	374
	300	330	300
2/18	332	375	332
	352	275	352
3/4	248	290	248
	230	260	230
3/18	230	230	230
	300	361	300
	332	375	332
	280	500	280
3/25	248	260	248
	300	330	300
4/1	285	375	285
	300	461	300
	285	332	285
	332	374	332
4/8	214	214	214
	214	214	214
	214	214	214
4/29	340	375	340

DISCUSSION

The frequent change from the auricular tachycardia into auricular fibrillation, and vice versa, which was observed during vagus stimulation or followed cooling or developed spontaneously, shows, in our opinion, that we are dealing with auricular flutter in these experiments and in those previously reported.[31] The appearance of "rapid re-excitation" was observed by Lewis even when the auricles were driven by artificial stimuli, but in tracings like those shown in Fig. 1 where auricular fibrillation persisted in an unchanged form long after the end of the vagus stimulation, we are dealing with simple auricular fibrillation. Clinically and experimentally the change from flutter to fibrillation and vice versa is a common event, while the change from auricular tachycardia to fibrillation or from fibrillation to a paroxysmal auricular tachycardia is practically

unknown. When an auricular tachycardia with a rate between 200 and 300 occurs after an attack of auricular fibrillation has been stopped by focal cooling, as shown in Fig. 3,*B*, and when this tachycardia changes within a few seconds into auricular fibrillation, we feel justified in calling this auricular tachycardia auricular flutter.

Our inability to stop the auricular tachycardia, even with the strongest faradic stimulation of a vagus nerve, is more readily understood if auricular flutter exists. The arrest of auricular flutter by vagus stimulation is unknown, while it is a common phenomenon in auricular tachycardia. This difference of response is one of the reasons why we are inclined to insist on separating the two conditions in spite of a recent tendency to regard them as identical. The auricular rate in auricular flutter has been found to be increased during vagus stimulation experimentally[22,29] and clinically.[35]

The interruption of the auricular fibrillation by cooling the area into which the injection was given, an area with a diameter of only a few millimeters, might be compatible with the circus movement theory of Lewis. Cooling prolongs the refractory phase[6] and in this way might end the circulation of the central wave. Actually, termination of fibrillation by perfusing the heart with a cool fluid has been observed[14,28] and, in a footnote of his book, Lewis remarked: "Fibrillation, like flutter may also on occasion be terminated by cold and pressure, very locally applied. All such effects presumably depend upon interference with a single circulating wave.[20] With the technique used by Lewis, who studied the short runs of fibrillation which follow faradization of the auricle, the reappearance of auricular fibrillation after its termination by cooling could not be observed. In our experiments the fibrillation invariably recurred as the cooling was stopped. Its reappearance cannot be explained if a circus movement proceeds up or down the taenia terminalis unless we accept the existence of a center for abnormal stimulus formation. If the presence of a center of formation of abnormal stimuli in these tracings is assumed, the conception of a circus movement, in the sense that Lewis used this term, can be abandoned. It might be proposed that forms of circus movement exist, such as, for instance, those suggested by Garrey[13] and Ashman and Hull.[1] It is, however, difficult to imagine how an injection of aconitine anywhere into the auricular wall should invariably lead to the special conditions which, according to these authors, are necessary to cause the appearance of circus waves.

We do not intend to imply, however, that circus movement or the phenomenon of re-entrance does not occur. This is known to exist in muscular rings in the frog heart between auricle and ventricle, in simple muscle strips,[32] and under special conditions even in the mammalian heart.[30,34]

If a circus movement is rejected and if we attribute the auricular flutter in these tracings to a rapid stimulus formation in a center, the increase of rate during vagus stimulation must be explained by a direct stimulating vagal action on the center. Rothberger and Winterberg,[29] who observed the increase of rate in auricular flutter during vagus stimulation, discarded this possibility in view of the well-known inhibitory action of the vagus on the different properties of the heart. These authors thought that the shortening of the refractory period

during vagus stimulation is in some way responsible for the increase of rate, but they gave no clear idea of how this could take place.

It has become clear in recent years that, coinciding with the inhibitory effects of the vagus on the contractility of the auricles and on conduction from the sinus node to the auricles and from the auricles to ventricles, other "positive" and, therefore, somewhat paradoxic effects of the vagus on the heart occur. They are, to some extent, encountered regularly and, in part, only under certain circumstances; repeatedly, the presence of accelerator fibers in the vagus has been postulated. Thus, increase of rate upon vagus stimulation was observed in the nicotinized mammalian heart.[4] Since the paradoxic effect appeared after a period of latency which was scarcely noticeable, an action of sympathetic fibers can be ruled out. The vagus does not inhibit conduction from fiber to fiber in auricular muscle.[22,25] If the intra-auricular conduction is impaired by cooling or pressure, vagus stimulation improves it and restores normal conditions.[21] The recovery of auricular tissue after conduction is extremely rapid during vagus stimulation.[8] If a complete block was produced within the auricular tissue by application of a clamp, and this lasted for forty minutes, it was immediately abolished by vagus stimulation.[21] This effect can hardly be explained by the shortening of the refractory phase alone. The excitability of the auricle during vagus stimulation, which for many years was believed to be depressed, was found to be augmented. This has been demonstrated repeatedly by determination of the chronaxie[10,11,17,27] and also by the threshold method.[10]

The finer mechanism of stimulus formation is unknown. Whether we assume a rhythmic formation of stimuli or a rhythmic response to a continuous stimulus, it is clear that the rate depends on the length of the refractory period and that a shortening of this period may increase the rate directly.[2]

Faradic stimulation of the right or left vagus nerve in the neck during auricular flutter elicited by the topical administration of aconitine to the auricular appendices invariably leads to a marked acceleration of rate.[31] In the series of experiments reported in this paper, however, the injection of aconitine into the region of the head of the sinus node and faradic stimulation, even with the secondary coil over the primary coil, failed in three experiments to alter the auricular rate or caused but a moderate increase of rate.

We consider it possible that whenever stimulation of the vagus nerves with the strongest faradic currents did not alter the rate of the flutter, or influenced it only slightly, the focus of stimulus formation was in the specific tissue of the sinus node. A focus in the muscle of the taenia terminalis responded in the same way as foci in the appendices, that is, with marked acceleration. The specific tissue of the sinus node and of the A-V conduction system has a refractory period which is about 30 per cent longer than that of the auricular muscle,[7,19] and its excitability as measured with the chronaxie method is about three times lower.[18] There is experimental evidence to favor the assumption that the refractory period of the specific tissue is less influenced by vagus stimulation than is that of the auricular muscle.[24]

On the basis of the available evidence we believe it is possible that auricular flutter and fibrillation are caused by rapid stimulus formation in one center.

With a rapid rate of stimulus formation, islands of refractory muscle appear, just as conceived by Porter and proved by Lewis and his collaborators. Due to the presence of these islands, local dissociations appear; re-entrant waves and local circus movements are made possible. These are not the cause of fibrillation but a concomitant feature. It is well known that it is impossible to cause auricular fibrillation by faradization of isolated specific tissue.[33] On the other hand, without specific tissue no fibrillation appears.[26] A certain muscle mass is necessary for the development of fibrillation.[12] We, therefore, conclude that specific tissue is necessary for the stimulus formation and that the muscle mass with the blocked areas leads to weaving and interweaving of stimuli traveling over the heart.

SUMMARY

Injection of aconitine into the region of the head of the sinus node causes auricular tachycardia with a rate between 200 and 400 per minute. Often auricular fibrillation appears spontaneously or follows vagus stimulation. The change of the auricular tachycardia into fibrillation and vice versa, which was often registered, shows that the auricular tachycardia is auricular flutter and not "paroxysmal auricular tachycardia."

Cooling of the focus of injection immediately abolishes the fibrillation which reappears when the cooling is interrupted. These results cannot be explained by the circus movement theory of Lewis. They can only be explained by assuming that auricular flutter and fibrillation are initiated by rapid impulse formation in a single center. As the impulses thus formed move into the larger mass of auricular muscle, islands of refractory tissue appear, which cause a weaving and interweaving of the contraction process that is characteristic of fibrillation.

The increase of auricular rate during vagus stimulation in the presence of auricular flutter is caused by a direct action of the vagus on the center of stimulus formation. Shortening of the refractory phase increases the rate of stimulus formation.

When flutter originates in the auricular appendices the increase in rate during vagus stimulation is greater than when it originates in the area of the sinus node. The vagus effect on the refractory phase seems to be less pronounced on specific tissue than on auricular muscle.

REFERENCES

1. Ashman, R., and Hull, E.: Essentials of Electrocardiography, ed. 2, New York, 1941, The Macmillan Company.
2. Brücke, E. T.: Vergleichende Physiologie des Erregungsvorganges, Ergebn. d. Biol. **6**:327, 1930.
3. Campbell, M.: Paroxysmal Tachycardia and 2:1 Heart Block, Brit. Heart J. **7**:183, 1945.
4. Dale, H. H., Laidlaw, P. P., and Symons, C. T.: A Reversed Action of the Vagus on the Mammalian Heart, J. Physiol. **41**:1, 1910.
5. Decherd, G. M., Jr., Herrmann, G. R., and Schwab, E. H.: Paroxysmal Supraventricular Tachycardia With A-V Block, Am. Heart J. **26**:446, 1943.
6. Drury, A. N.: Further Observations Upon Intra-auricular Block Produced by Pressure or Cooling, Heart **12**:143, 1925.
7. Drury, A. N., and Brow, G. R.: Observations Relating to the Unipolar Electrical Curves of Heart Muscle With Especial Reference to the Mammalian Auricle, Heart **12**:321, 1926.

8. Drury, A. N., and Regnier, M.: Observations Upon Conduction in the Mammalian Heart, Heart **14**:263, 1928.
9. Evans, W. J.: The Unity of Paroxysmal Tachycardia and Auricular Fibrillation, Brit. Heart J. **6**:221, 1944.
10. Field, H., Jr., and Brücke, E. T.: Erregbarkeit und Chronaxie des Herzens während der Vaguswirkung, Arch. f. d. ges. Physiol. **213**:715, 1926.
11. Fredericq, H.: Recherches chronaximétriques relatives au mécanisme humoral de l'action du vagosympathique sur l'excitabilité du coeur des poikilothermes, Arch. internat. de physiol. **24**:294, 1925.
12. Garrey, W. E.: The Nature of Fibrillary Contraction of the Heart; Its Relation to Tissue Mass and Form, Am. J. Physiol. **33**:397, 1914.
13. Garrey, W. E.: Auricular Fibrillation, Physiol. Rev. **4**:215, 1924.
14. Gley, M. E.: Contribution à l'étude des mouvements rhythmiques des ventricules cardiaques, Arch. de physiol. norm. et path. 5. s. **3**:735, 1891.
15. Lapicque, M., and Fredericq, H.: Chronaxie du ventricule et du faisceau de His chez le chien, Arch. internat. de physiol. **23**:93, 1924.
16. Lapicque, M., and Veil, C.: Vitesses musculares mesurées par la chronaxie dans les différentes cavités du coeur et les faisceaux de passage, Compt. rend. Acad. d. sc. **163**:103, 1916.
17. Lapicque, M., and Veil, C.: Modifications de la chronaxie du ventricule et du faisceau auriculoventriculaire pendant l'excitation du pneumogastrique, Compt. rend. Soc. de biol. **91**:1207, 1924.
18. Lapicque, M., and Veil, C.: Chronaxie des fibres de Purkinje dans le coeur de divers mammiferes, Ann. de physiol. **1**:178, 1925.
19. Lewis, T.: The Law of Cardiac Muscle With Special Reference to Conduction in the Mammalian Heart, Quart. J. Med. **14**:339, 1921.
20. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1925, Shaw & Sons, Ltd.
21. Lewis, T., and Drury, A. N.: The Effect of Vagal Stimulation on Intra-auricular Block Produced by Pressure or Cooling, Heart **10**:179, 1923.
22. Lewis, T., Drury, A. N., and Bulger, H. A.: Flutter and Fibrillation; the Effects of Vagal Stimulation, Heart **8**:141, 1921.
23. Lewis, T., Drury, A. N., and Iliescu, C. C.: Some Observations Upon Atropine and Strophanthin, Heart **9**:21, 1921.
24. Lewis, T., and Master, A. M.: Observations Upon Conduction in the Mammalian Heart; A-V Conduction, Heart **12**:209, 1925.
25. Lewis, T., Meakins, J., and White, P. D.: The Excitatory Process in the Dog's Heart. I. The Auricles, Phil. Tr., London, Series B **205**:375, 1914.
26. Nomura, S.: On the Function of the "Reizleitungssystem" in the Heart, Mitt. a. d. med. Fakult. d. k. Univ. Kyushu Fukuoka, **9**:195, 1924.
27. Nowinski, V. W.: Einfluss der Vagusreizung auf die Erregbarkeit der verschiedenen Herzabschnitte, Ztschr. f. Biol. **91**:152, 1930.
28. Porter, W. T.: Recovery of the Heart From Fibrillatory Contractions, Am. J. Physiol. **1**:71, 1898.
29. Rothberger, C. J., and Winterberg, H.: Ueber Vorhofflimmern und Forhofflattern, Arch. f. d. ges. Physiol. **160**:42, 1914.
30. Scherf, D.: An Experimental Study of Reciprocating Rhythm, Arch. Int. Med. **67**:372, 1941.
31. Scherf, D.: Studies on Auricular Tachycardia Caused by Aconitine Administration, Proc. Soc. Exper. Biol. & Med. **64**:233, 1947.
32. Schmitt, F. O., and Erlanger, J.: Directional Differences in the Conduction of the Impulse Through Heart Muscle and Their Possible Relation to Extrasystolic and Fibrillary Contractions, Am. J. Physiol. **87**:326, 1928.
33. Wachstein, M.: Untersuchungen am Purkinjefaden, Ztschr. f. d. ges. exper. Med. **83**:491, 1932.
34. Wiggers, C. J.: Physiology in Health and Disease, ed. 4, Philadelphia, 1944, Lea & Febiger.
35. Wilson, F. N.: Report of a Case of Auricular Flutter in Which Vagus Stimulation Was Followed by an Increase in the Rate of the Circus Rhythm, Heart **11**:61, 1924.

CELLOPHANE TREATMENT OF SYPHILITIC ANEURYSMS WITH REPORT OF RESULTS IN SIX CASES

J. K. Poppe, M.D.
Portland, Ore.

ALTHOUGH syphilitic aneurysms of the thoracic aorta may possibly become nonexistent within the next few decades of penicillin therapy, a sufficient number still persist, expand, and rupture to warrant adoption of a practical and relatively simple surgical treatment. The limited applicability, poor results, and numerous fatal complications accompanying the various blind wiring techniques of aneurysms led to their almost complete abandonment over a decade ago.

The distorted anatomy, invasive tendencies, large size, and friable, thin walls of these aneurysms contraindicate any attempt at extensive surgical manipulation in the form of resections or anastomoses. The pounding, pulsating pressure exerted by these aortic dilatations presents an almost malignant tendency to invade and penetrate any adjacent soft tissue. Ordinary soft tissues offer little resistence, and even the ribs and sternum can be eroded by an expanding, pulsating aneurysm.

The intense foreign body reaction produced by cellophane with its constricting fibrosis seemed to offer the simplest and most satisfactory method of at least curbing the expansion, and possibly constricting these aneurysmal dilatations. This possibility was suggested by the report of Harrison and Chandy[1] who had gradually eliminated two arteriovenous aneurysms of the subclavian vessels by cellophane. Harrison's clinical application of the material was in turn suggested by Pearse,[2] who had demonstrated the ability of cellophane as an improved method of gradual obliteration of the lumen of important blood vessels, such as the internal carotid, in the place of the previously devised and somewhat unsatisfactory clamps and bands. This constricting property of cellophane had been demonstrated originally by Page,[3] who used it in 1939 to produce artificial nephritis and hypertension in dogs by wrapping it around the kidneys.

A dilemma arose, however, from the reports of McKeever[4] and others that cellophane produced no reaction and was suitable for reconstructing tendon sheaths and lining joint spaces. An experimental study was undertaken at Washington University School of Medicine with several representative chemically different varieties of cellophane, supplied through the courtesy of the DuPont de Nemours Company of Wilmington, Del. The results of this in-

Received for publication Sept. 2, 1947.

vestigation, published in greater detail elsewhere,[5] suggested that a new type known as Polythene cellophane produced the most intense fibrotic foreign body reaction, whereas some of the other types produced little if any reaction.*

Polythene cellophane was selected, therefore, to wrap syphilitic aneurysms of the thoracic aorta to induce an intense, foreign-body fibrous tissue reaction around the aneurysm, thereby preventing its further expansion and eventual rupture. It was hoped also that the constrictive action of the scar tissue might even reduce the already existing dilatation of the lumen of the aneurysm.

OPERATIVE TECHNIQUE EMPLOYED

Under endotracheal anesthesia the patient is placed on the side opposite the aneurysmal dilatation of the thoracic aorta. Through a paravertebral incision extending around the angle of the scapula, the entire length of the fifth or sixth rib is resected and the pleura opened through the bed of the resected rib. The lung is retracted and the mediastinal pleura dissected free from the aneurysm, exposing as much of the surface of diseased aorta as can be safely freed without danger of rupture. It is frequently impossible to free the entire circumference of the descending aorta because of beginning erosion of the vertebrae and ribs around the origins of the intercostal vessels. The pleura may also be too attenuated and adherent over thin bulging areas to permit its complete removal. A sheet of Polythene cellophane is then cut to fit the dilated portion of aorta without extending over adjacent normal structures. This cellophane is sutured loosely to any suitable mediastinal tissue with fine silk sutures, care being taken not to pass any sutures directly into the wall of the aneurysm.

SUMMARY OF RESULTS

Polythene cellophane was used to wrap the six syphilitic aneurysms of the thoracic aorta reported in Table I.

The last two patients included in the table were treated too recently to permit any definite evaluation of their symptoms, and although they both claim to feel slightly improved, this may be primarily psychologic. Two other aneurysms of the ascending aorta were wrapped at the St. Louis City Hospitals in 1945, but these patients are believed to have died since that time without post-mortem examinations having been performed. One other aneurysm of the ascending aorta was explored at the Portland Veterans' Administration Hospital in 1947, but found unsuitable for wrapping because of erosion of the anterior chest wall to such a degree that cellophane could not be applied to the surface of the aneurysm. Several other patients have been considered unsuitable for surgery, either because of severe cardiac decompensation or complete obstruction of the left main bronchus by pressure from the aneurysm.

*In consideration of the recent reports on the nonreactive nature of pure Polythene, I wish to stress that an impure film was used in the experimental and clinical results reported in this paper. This film was obtained from the Technical Service Laboratory of the Cellophane Division of the E. I. DuPont de Nemours and Company of Wilmington, Del., and contained no plasticizer or antioxidant material. Other substances were included in the film which were considered essential to the manufacturing process, the nature of which cannot be disclosed.

TABLE I. THE FINDINGS IN SIX PATIENTS WHOSE ANEURYSMS WERE WRAPPED WITH POLYTHENE CELLOPHANE

NO.	NAME	DATE	PLACE	TYPE	LOCATION	SYMPTOMS	RESULT
1	W. W.	7/6/45	Barnes Hosp., St. Louis, Mo.	Fusiform	Descending	Pain in anterior and posterior chest	Complete relief of pain
2	J. E.	12/8/45	Barnes Hosp., St. Louis, Mo.	Saccular and fusiform	Ascending aorta and innominate artery	Chest pain and weakness	Relief of pain, but weakness remains
3	F. K.	11/29/46	Good Samaritan Hosp., Portland, Ore.	Fusiform*	Distal arch and descending aorta	Chest pain and cough	Relief of chest pain
4	W. H.	1/16/47	Veterans' Hosp., Portland, Ore.	Fusiform	Distal arch and descending aorta	Chest pain	Complete relief of pain
5	J. L.	6/28/47	County Hosp., Portland, Ore.	Fusiform	Distal arch and descending aorta	Chest pain, hemoptysis, chronic cough, and dyspnea	
6	C. E.	7/10/47	Veterans' Hosp., Portland, Ore.	Saccular and fusiform	Ascending aorta	Anginoid pain on exertion	

*See Fig. 1.

COMMENTS

Although the chief purpose of cellophane wrapping of aneurysms is prophylactic and is intended to prevent their further expansion and eventual rupture or erosion into adjacent vital structures, it has been proved also to eliminate some of the already existing symptoms of aching and throbbing pain in the chest. As yet no pathologic material is available to determine whether or not an actual shrinking of the lumen occurs. However, the continued existence and improvement of symptoms in the four patients who have now been followed for two years would seem to indicate a reduction of expansion and pulsation in these individuals without any deleterious effects from undue constriction or obliteration of the lumen. The lack of decrease in size of the x-ray shadows is to be expected from the pathologic reaction noted in animals in which a thick layer of dense scar tissue is deposited on both sides of the cellophane.

The most favorable results have been obtained in fusiform aneurysms of the descending thoracic aorta (Fig. 1) where it is almost possible to encircle the dilatation completely without encountering other vital structures or major arterial

branches. The relief of the severe aching and throbbing pain produced by these lesions offers more comfort to the average syphilitic patient than the assurance that an asymptomatic aneurysm is no longer likely to grow larger or rupture.

At present, contraindications to surgery appear to consist of bronchial obstruction or erosion from pressure, severe heart disease with aortic insufficiency and decompensation, or erosion of the anterior chest wall. Arteriosclerotic aneurysms appear less suitable for surgical treatment than syphilitic aneurysms in view of the generalized distribution of the disease, advanced age of the patients, frequent location of the dilatation in the abdominal aorta with involvement of vital visceral branches, and frequently absent pulsation in the extremities.

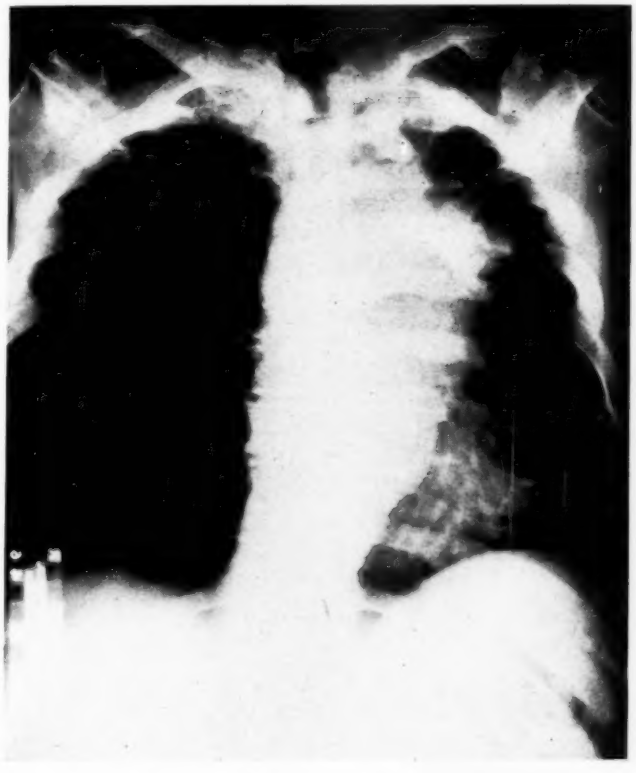

Fig. 1.—Fusiform type of aneurysm of distal arch and descending aorta which has proved most suitable for cellophane wrapping to reduce chest pain (Patient 3, F. K.).

CONCLUSIONS

1. Polythene cellophane produces a dense fibrous tissue reaction which can be applied to aortic aneurysms to curb their pulsations, expansion, and tendency to rupture.

2. Six patients have been reported whose thoracic aortic aneurysms have been successfully treated by cellophane wrapping.

3. Relief of chest pain has been noted without deleterious effects from the cellophane during periods ranging from a few months to two years.

4. Indications and contraindications for surgical treatment of syphilitic intrathoracic aortic aneurysms have been mentioned.

5. The importance of selecting the proper type of cellophane to produce fibrosis cannot be emphasized too strongly, since certain varieties incite little or no foreign body reaction.

REFERENCES

1. Harrison, P. W., and Chandy, J.: Subclavian Aneurysm Cured by Cellophane Fibrosis, Ann. Surg. **118**:478, 1943.
2. Pearse, Herman E.: Experimental Studies on Gradual Occlusion of Large Arteries, Ann. Surg. **112**:923, 1940.
3. (a) Page, I. H.: Production of Persistent Hypertension by Cellophane, J. A. M. A. **113**: 2046, 1939.
   (b) Page, I. H.: Method for Producing Persistent Hypertension by Cellophane, Science **89**:273, 1939.
4. McKeever, D. C.: Use of Cellophane as Interposition Membrane in Synovectomy, J. Bone & Joint Surg. **25**:576, 1943.
5. Poppe, J. K., and Renault de Oliveira, H.: Treatment of Syphilitic Aneurysms by Cellophane Wrapping, J. Thoracic Surg. **15**:186, 1946.

THE MECHANISM OF IRREGULAR SINUS RHYTHM IN AURICULOVENTRICULAR HEART BLOCK

IRVING R. ROTH, M.D., AND BRUNO KISCH, M.D.
NEW YORK, N. Y.

IT HAS long been known that in auriculoventricular heart block, partial or complete, the auricles often exhibit an irregular rhythm. When such an irregularity exists, the auricular intervals which embrace ventricular systole are generally the shortest while those that follow in the wake of a ventricular systole are the longest. As illustrated in Figs. 1, 2, and 3, the irregularity is essentially a sinus arrhythmia, characterized by postsystolic slowing of the auricles. In these and subsequent figures and corresponding tables, auricular systole is indicated by the letter *P* and the initial graphic evidence of ventricular systole by the letter *Q*, no matter what its direction, negative or positive. Accordingly, *PQP* designates an auricular interval which contains the initial ventricular deflection and *P-P* designates an auricular interval devoid of such a deflection. Either the *PQP* or the *P-P* or both may contain a part or all of the terminal portion of the ventricular complex.

The point *Q* has been chosen because in a complete heart block, where QRS complexes are bizarre and wide, the peaks of R waves may be poorly defined and may not appear in the graph anywhere from 0.04 to 0.08 second after the onset of systole. Representing the initial deflection in the ventricular complex more accurately, the *Q* can serve as a point of reference from which measurements might be made in order to establish a time relation between the onset of ventricular systole and the onset of the initial and terminal P waves bounding intervals which contain it. Such time relations are designated in the tables as the *PQ* and *QP* segments of *PQP* intervals. As will be pointed out, a knowledge of the relative durations of these segments is important in determining the effect of ventricular systole, if any, upon the auricular pacemaker.

The pattern of the auricular irregularity in A-V heart block, although essentially a postsystolic slowing of the auricles, varies with the degree of the block In the first part of Fig. 1, for example, where a 3:1 partial block is illustrated, it will be observed that, although auricular cycle-lengths vary from beat to beat, they manifest an orderly, cyclic grouping in relation to ventricular systole. In each recurrent group of three cycles, beginning with an interval, *PQP*, which contains the initial ventricular complex (all of systole in this graph) the *PQP* interval is the shortest, the first *P-P* interval is the longest, and the cycle-length of the second *P-P* is intermediate. In a complete heart block as illustrated in Fig. 2, on the other hand, auricular rhythm may appear totally irregular be-

Received for publication July 21, 1947.

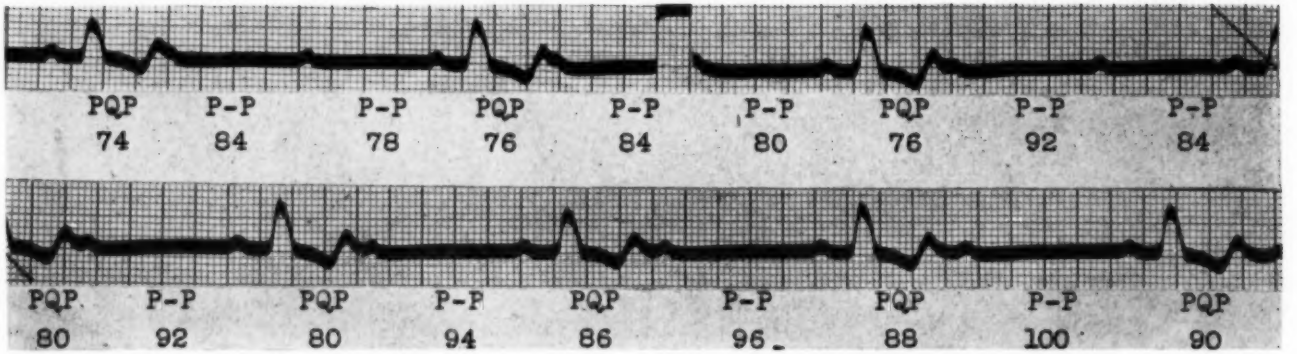

Fig. 1.—3:1 partial A-V heart block, changing abruptly to a 2:1 ratio. Auricular intervals irregular. However, *PQP* is always shortest; first *P-P* the longest; and second *P-P* (upper graph) is intermediate. Unit of measure = 0.01 second. (Graph corresponds to Cycles 22 to 39 in Table I.)

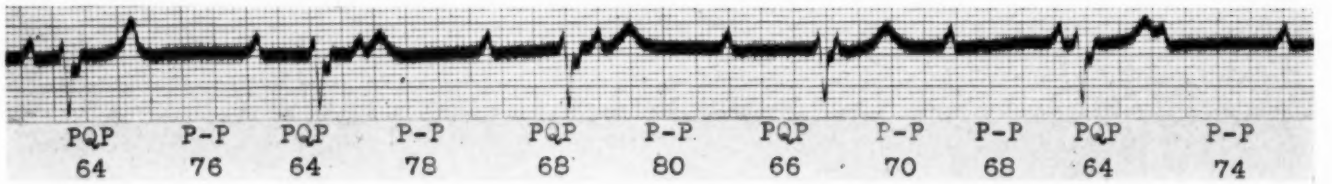

Fig. 2.—Complete A-V heart block. Ventricular rate, approximately 38.5 per minute; QRS-T interval, 0.52 second. Auricular intervals vary between 0.64 and 0.80 second. Note durations of second, fourth, and sixth postsystolic *P-P* intervals. Unit of measure, 0.01 second. (Graph corresponds to Cycles 6 to 16 in Table II.)

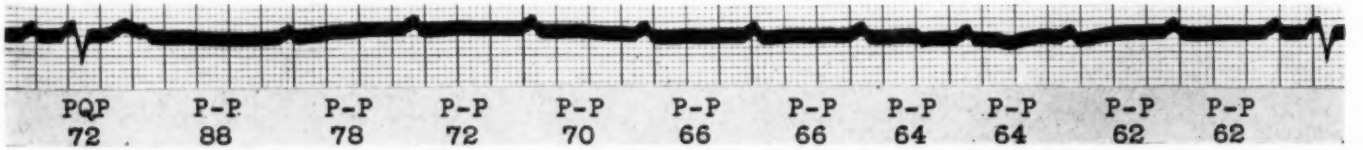

Fig. 3.—A span of ventricular standstill of 7.64 seconds' duration. Increase of first *P-P* over preceding *PQP* is more than 22 per cent. Slowing is then seen to vanish gradually over several cycles. Unit of measure, 0.01 second. (Graph corresponds to Cycles 19 to 29 in Table III.)

cause of dissociation between auricles and ventricles. Still another pattern appears in Fig. 3 where a ventricular standstill of 7.64 seconds is illustrated. In this figure, postsystolic slowing is seen to vanish gradually over a series of several cycles. These patterns are especially evident in Tables I, II, and III where measurements of the durations of *PQ* and *QP* segments, *PQP* and *P-P* intervals, first and subsequent ones, if any, are listed. The per cent increase of first *P-P* intervals over *PQP* intervals immediately preceding them are recorded in the last column of each table.

TABLE I. MEASUREMENTS OF THIRTY-NINE CONSECUTIVE AURICULAR INTERVALS IN A PARTIAL A-V HEART BLOCK, THE LAST EIGHTEEN OF WHICH ARE ILLUSTRATED IN FIG. 1. THE 3:1 A-V RATIO CHANGES ABRUPTLY, IN THE THIRTY-FIRST CYCLE TO A 2:1 RATIO. UNIT OF MEASURE, 0.01 SECOND

NO.	PQ	QP	PQP	P-P	% INCREASE
1	24	44	68		
2				80	17.65
3				72	
4	24	44	68		
5				80	17.65
6				72	
7	24	44	68		
8				76	11.76
9				72	
10	24	42	66		
11				82	24.24
12				74	
13	24	44	68		
14				80	17.65
15				72	
16	24	48	72		
17				84	16.67
18				76	
19	24	48	72		
20				84	16.67
21				80	
22	24	50	74		
23				84	13.51
24				78	
25	24	52	76		
26				84	10.53
27				80	
28	24	52	76		
29				92	21.05
30				84	
31	24	56	80		
32				92	15.00
33	24	56	80		
34				94	17.50
35	24	62	86		
36				96	11.63
37	24	64	88		
38				100	13.64
39	24	66	90		

PQ and *QP* are component segments of *PQP* intervals. Average duration of *PQP*, 0.74 second; of first *P-P* 0.86 second; of second *P-P*, 0.76 second. Average increase of first *P-P* over preceding *PQP* is approximately 16 per cent.

The auricular irregularity illustrated in the figures and tables is, we believe, peculiar to A-V heart block and will form the basis of our discussion. Coincidental irregularities such as premature beats, auricular flutter, and fibrillation, for example, are not included in this study. We are concerned with irregular sinus rhythms which, we believe, are related to and provoked by the circulatory dynamics of the heart block in which they are encountered. It is our purpose to establish a comprehensive concept to account for the physiologic mechanism of this arrhythmia.

TABLE II. MEASUREMENTS OF THIRTY-ONE CONSECUTIVE AURICULAR INTERVALS IN A COMPLETE A-V HEART BLOCK, CYCLES 6 TO 16 OF WHICH ARE ILLUSTRATED IN FIG. 2. UNIT OF MEASURE, 0.01 SECOND

NO.	PQ	QP	PQP	P-P	% INCREASE
1	64	8	72		
2				74	2.78
3				74	
4	4	64	68		
5				74	8.82
6	24	40	64		
7				76	18.75
8	38	26	64		
9				78	21.88
10	50	18	68		
11				80	17.65
12	56	10	66		
13				70	6.06
14				68	
15	12	52	64		
16				74	15.63
17	32	34	66		
18				80	21.21
19	42	28	70		
20				82	17.14
21	44	24	68		
22				78	14.71
23	56	14	70		
24				74	5.71
25	68	2	70		
26				70	0.00
27				68	
28	20	44	64		
29				76	18.75
30	36	30	66		
31				80	21.21

PQ and *QP* segments vary widely (dissociation). Auricular intervals, *PQP* and *P-P*, vary between 0.64 and 0.82 second. Average duration of first *P-P*, 0.76 second; of *PQP* 0.67 second; average increase of first *P-P* over *PQP*, approximately 13.5 per cent.

Irregular auricular action was first observed in experimental heart block in 1910 by Erlanger and Blackman[1] who assigned it to an increased vagal tone, enhanced by the arterial pulse. The first clinical case, that of a child suffering from Stokes-Adams seizures, was reported in 1914 by Hecht.[2] That the auricular arrhythmia tends to disappear on acceleration of the heart rate as a result of exercise or atropine administration was demonstrated by Wilson and Robinson[3]

in 1918. A decade later, Wenckebach and Winterberg[4] advanced the opinion that in A-V heart block improved nutrition of the sinoauricular node, as a result of ventricular systole, raises its potentiality for impulse production while impaired nutrition during ventricular diastole depresses the pacemaker. Aside from the foregoing views, there have been suggestions to the effect that the contracting ventricles might, by mechanical stimulation, enhance impulse production at the site of the normal pacemaker in a manner similar to what presumably occurs when premature auricular beats are provoked by mechanical stimulation of ectopic auricular foci during ventricular contractions in heart block. Accord-

TABLE III. MEASUREMENTS OF TWENTY-NINE CONSECUTIVE AURICULAR CYCLES IN A PARTIAL A-V HEART BLOCK WITH PERIODIC PROFOUND VENTRICULAR STANDSTILL. CYCLES 19 TO 29 ARE ILLUSTRATED IN FIG. 3. UNIT OF MEASURE, 0.01 SECOND

NO.	PQ	QP	PQP	P-P	% INCREASE
1	24	64	88		
2				92	4.54
3	24	56	80		
4				88	10.00
5	24	56	80		
6				90	12.50
7				80	
8				76	
9				74	
10	52	18	70		
11				74	5.71
12				72	
13	28	40	68		
14				70	2.91
15				68	
16	26	42	68		
17				76	11.81
18				72	
19	24	48	72		
20				88	22.22
21				78	
22				72	
23				70	
24				66	
25				66	
26				64	
27				64	
28				62	
29				62	

Cycle 5 initiates a ventricular standstill of 4.28 seconds; Cycle 19 initiates one of 7.64 seconds. During standstill, auricular slowing, most marked in first *P-P* intervals, vanishes gradually over several cycles.

ing to the observations of Wolferth and McMillan,[5] auricular premature beats, on the analogy of which this concept is based, cannot be satisfactorily explained on the assumption of mechanical stimulation of auricles by ventricles, but rather on the basis of retrograde conduction of the excitatory process through the area of block.

In recent years, it has become more and more apparent that a reflex vagus effect, as postulated by earlier observers, is a factor in the production of auricular

arrhythmia in A-V heart block. Graybiel and White,[6] for example, impressed with the fact that in ventricular standstill for two or more auricular cycles the one following ventricular systole is the longest while subsequent ones are of shorter duration, expressed the opinion that "under certain conditions ventricular systole increases vagal tone, possibly through the carotid sinus mechanism or directly through the arterial impulse in the sinoauricular artery or otherwise." They believed this was the usual mechanism. Shortly thereafter, but apparently independently, Kisch[7] came to a similar but more comprehensive conclusion. On the basis of a detailed study of a complete A-V block and in the light of the physiology of reflex vagus and accelerator effects upon the cardiac pacemaker, he postulated that a vagus-sympathetic reflex along aortic and carotid sinus pathways constitutes the mechanism responsible for postsystolic auricular slowing in A-V heart block. Recent observations of Fatzer[8] are in agreement with this opinion.

Apparently with a view to a critical appraisal of theories previously advanced, Parsonnet and Miller[9] reported observations in thirty-eight cases of heart block, twenty-eight complete and ten partial. They concluded that although each of the former theories "may embody factors" which, in part, account for the irregular auricular mechanism in heart block, "the reflex mechanism which is involved is unknown." Their criticism of "former theories" was based essentially on the following: (1) that they failed to account for the fact that the lengths of auricular intervals in heart block appeared to be "independent of the point of incidence of ventricular systole"; and (2) that they failed to explain "exceptions to the rule," namely, cases in which an auricular interval containing the initial ventricular complex (*PQP*) is longer than an adjacent interval devoid of such a complex (*P-P*); or cases in which there is "no correlation at all" between these two types of auricular intervals. Since in the light of their criticsm no former theory fully accounted for the auricular irregularity encountered in heart block, these authors suggested that the length of auricular intervals during ventricular diastole in heart block might be determined by the relative dominance of two opposing forces. One of these is a depression of the pacemaker as a result of the "absence of the stimulus from the contracting ventricle"; the other, a Bainbridge reflex.

We take no exception to the foregoing criticism as far as it concerns the view advanced by Wenckebach and Winterberg. This is untenable, on the whole, because it is contrary to the known fact that auricular slowing in heart block generally occurs in the wake of an effective ventricular contraction when cardiac nutrition is presumably at its best. If one assumes, however, that auricular arrhythmia when present is due to a reflex vagus effect, the criticism does not apply. The fact that auricular irregularity is not always present and that when it is present a clear-cut correlation between auricular cycle-length and the point of incidence of ventricular systole is not readily demonstrable does not mitigate against the concept that in A-V heart block the auricular pacemaker is under the influence of a reflex vagus mechanism. Such a mechanism is labile, subject to many intrinsic and extrinsic factors, and since its influence

usually endures over several auricular cycles its effects are often obscured. Even the degree of the heart block may obscure it.

In complete heart block, for example, the rhythm of the auricles may appear so irregular as to create the impression of an utter lack of correlation. However, this seeming total irregularity is precisely what might be deemed to serve as evidence of correlation. Since in complete dissociation auricular contraction may precede, coincide with, or follow auricular contractions, the degree of ventricular effect upon auricular cycle-lengths, if any, must be highly variable. Careful measurements of *QP* segment-lengths and subsequent *P-P* cycle-lengths are required to demonstrate the influence of ventricular systole upon the auricular rhythm.

The degree of ventricular effect upon an auricular interval would depend, in part at least, upon the element of time during which ventricular influence effectively operates. The condition for an optimal effect would clearly be a *QP* time relationship which would permit ventricular systole to exert its maximal influence upon the early phase of the next impulse production period at the S-A node and thus delay the terminal P wave of the postsystolic *P-P* interval, as indicated in the pattern, (P.....*Q*.*P*.....P). A lesser ventricular effect would be represented by a pattern in which the Q is not quite so close to the first P wave of the P-P interval, (P....*Q*...*P*.....P). By the same token, *PQP* intervals should themselves be least affected unless the Q appears very early in the interval, in which case the ventricular effect would be exerted largely upon the terminal P of the *PQP* and to a lesser degree upon the next *P-P* interval, (P.*Q*.....*P*.....P). Such patterns depicting the relationship between *QP* segment-lengths and auricular cycle-lengths we have repeatedly observed as conspicuous features of the auricular irregularity which accompanies A-V heart block. Such observations have led us to believe that the variation in auricular cycle-length which constitutes the auricular arrhythmia is, in part at least, a function of the point of incidence of ventricular systole.

Fig. 4 illustrates these features. Four of the eleven auricular cycles illustrated, namely, Cycles 3, 5, 8, and 10, are *P-P* intervals. Their respective cycle-lengths are 1.04, 1.00, 1.08, and 0.96 second. As listed in Table IV,*A*, the *QP* segments preceding the two longer cycles, 3 and 8, are relatively short, 0.10 and 0.18 second, respectively; while *QP* segments which precede the two shorter cycles, 5 and 10, are relatively long, 0.48 and 0.56 second. The fact that short *QP* segments are followed by long *P-P* intervals and long *QP* segments by short *P-P* intervals suggests that the duration of *P-P* intervals and the duration of the *QP* segments within *PQP* intervals immediately preceding them are related by an inverse ratio. Examination of large numbers of consecutive auricular cycles actually bears this out and tends to suggest, furthermore, that in a measure the relationship is a quantitative one.

Revealing in this connection is an analysis of Table IV in which measurements of three consecutive electrocardiograms, *A*, *B*, and *C*, are recorded from the same patient, representing a total of 128 auricular cycles. It will be recalled that the first eleven cycles of Tracing *A* are illustrated in Fig. 4. Of these 128

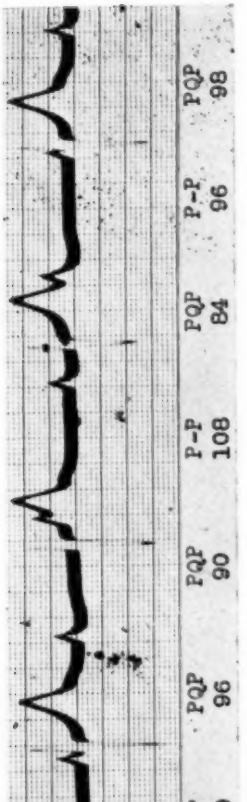

Fig. 4.—Complete A-V heart block. Ventricular rate approximately 38.5 per minute; QRS-T = 0.52 second. Auricular intervals totally irregular.

P-P intervals which follow close in the wake of ventricular systole, Cycles 3 and 8, are longer; those farther removed from ventricular systole, Cycles 5 and 10, are shorter. The one farthest removed, Cycle 10, is the shortest.

Note the exceptions to the rule implied in these *PQ* relationships: (1) The *P-P* in Cycle 3, although closest to ventricular systole, is not the longest; (2) Cycle 11, although a *PQP*, is longer than the preceding *P-P*.

Optimal *QP* segments for maximal ventricular effects are discussed in the text. (Graph corresponds to Cycles 1 to 11 in Column *A* of Table IV.)

auricular cycles, seventy-three are *PQP* intervals. There are six cycles which either terminate or begin with merged auricular and ventricular complexes in which the P wave is obscured by the QRS. These are designated as *PQ* or *QP* intervals and will not be considered.

The remaining forty-nine auricular cycles are *P-P* intervals. On viewing the table, it is at once apparent that although the durations of these vary to a wide degree, they are, on the whole, appreciably longer than the duration of the *PQP* intervals which precede them. The average duration of the forty-nine *P-P* intervals is approximately 0.99 second while the average duration of forty-nine *PQP* intervals immediately preceding them is approximately 0.87 second. The average increase of *P-P* intervals over their preceding *PQP* intervals is approximately 14 per cent.

More interesting is the fact that when the forty-nine *P-P* intervals are broken down into subgroups on the basis of cycle-lengths and the average *QP* segments in the preceding *PQP* intervals are calculated for each subgroup, a quantitative inverse relationship of *P-P* cycle-length to preceding *QP* segment-lengths is noted. Of the forty-nine *P-P* cycles contained in the three sections of Table IV, there are twenty-three whose cycle-lengths are 0.98 second or less, the average being 0.95 second. The average duration of *QP* segments preceding this subgroup is approximately 0.47 second. The cycle-lengths of the remaining twenty-six *P-P* intervals measure 1.00 second and over, the average being slightly above 1.02 seconds. The average duration of *QP* segments preceding these longer *P-P* intervals is less than 0.23 second. Since the average duration of the twenty-six longer *P-P* intervals was approximately 1.02 seconds, all *P-P* intervals with cycle-lengths of 1.02 seconds and over were further analyzed. Of these, the table contains fifteen with cycle-lengths ranging between 1.02 and 1.08 seconds, the average being approximately 1.04 seconds. The average *QP* segment preceding these longest P-P intervals is only 0.17 second.

An analysis of Table IV confirms, then, what has been suggested by its corresponding Fig. 4. The table discloses not only that *P-P* intervals, on the whole, are longer than the *PQP* intervals which precede them, but also that the shorter the *QP* segment within a systolic *PQP* interval, the longer is the duration of the subsequent diastolic *P-P* interval and that, therefore, these two variables are related by a quantitative inverse ratio. This analysis convincingly demonstrates that the time-segment, *QP* which elapses between the onset of ventricular systole and the onset of the auricular systole which signals the beginning and constitutes the initial boundary of the next *P-P* interval, is a factor in determining the duration of that interval.

Observations such as these have led us to support the view that post-systolic auricular slowing in A-V heart block, when present, is the result of a reflex vagus effect initiated by the arterial pulse. The physiologic mechanism proposed is that of a reflex inhibition of the auricular pacemaker, initiated by a pressure rise within the aorta and carotid arteries incident to the systolic injection of these vessels. Such an aortic and carotid sinus reflex alone, it would seem, could account for the fact that auricular slowing in heart block generally

TABLE IV. MEASUREMENTS OF THREE CONSECUTIVE ELECTROCARDIOGRAMS A, B, AND C, IN A COMPLETE A-V HEART BLOCK, COMPRISING A TOTAL OF 128 AURICULAR CYCLES. CYCLES 1 TO 11 OF TRACING A ARE ILLUSTRATED IN FIG. 5

NO.	A					NO.	B					NO.	C				
	PQ	QP	PQP	P-P	% INCR.		PQ	QP	PQP	P-P	% INCR.		PQ	QP	PQP	P-P	% INCR.
1	16	72	88			1	8	90	98			1	22	62	84		
2	86	10	96			2	68	22	90			2				92	9.52
3				104	8.33	3				108	20.00	3	4	80	84		
4	38	48	86			4	28	58	86			4	72	16	88		
5				100	16.28	5	98					5				98	11.36
6	10	86	96			6		98				6	40	42	82		
7	72	18	90			7	58	32	90			7				84	2.44
8				108	20.00	8				100	11.11	8	24	52	76		
9	28	56	84			9	26	62	88			9				92	21.05
10				96	14.29	10				94	6.82	10	8	76	84		
11	6	92	98			11	4	86	90			11	76	12	88		
12	66	24	90			12	68	18	86			12				104	18.18
13				104	15.56	13				102	18.60	13	36	48	84		
14	30	54	84			14	32	52	84			14				100	19.05
15				96	14.29	15				96	14.29	15	8	80	88		
16	6	90	96			16	8	80	88			16	80	12	92		
17	68	20	88			17	72	14	86			17				108	17.39
18				104	18.18	18				102	18.60	18	36	52	88		
19	32	54	86			19	36	48	84			19				100	13.64
20				98	13.95	20				96	14.29	20	12	76	88		
21	6	90	96			21	14	70	84			21	84	8	92		
22	68	20	88			22	80	6	86			22				102	10.86
23				102	15.91	23				100	16.29	23	44	42	86		
24	34	52	86			24	44	42	86			24				96	11.63
25				98	13.95	25				98	13.95	25	20	64	84		
26	10	76	86			26	16	68	84			26				92	9.52
27	80	8	88			27	84	8	92			27	4	84	88		
28				102	15.91	28				100	8.70	28	72	14	86		
29	44	44	88			29	44	42	86			29				96	11.63
30				102	15.91	30				98	13.95	30	28	56	84		

31	12	74	86			31	60	24	84			31				94	11.90
32	82	6	88			32	88	4	92			32	20	62	82		
33				98	11.36	33				100	8.70	33				92	12.20
34	52	34	86			34	44	40	84			34	8	80	88		
35				102	18.60	35				100	19.05	35	76	12	88		
36	22	62	84			36	20	64	84			36				100	13.64
37	96					37	94										
38		96				38		94									
39	60	28	88			39	52	32	84								
40				104	18.18	40				96	14.29						
41	24	60	84			41	28	56	84								
42				94	11.90	42				96	14.29						
43	4	96	100			43	4	84	88								
44	58	30	88			44	68	16	84								
45				100	13.64	45				100	19.05						
						46	38	46	84								
						47				96	14.29						

Columns A, B, and C contain a total of forty-nine *P-P* intervals. Their average duration is 0.99 second. Average duration of forty-nine *PQP* intervals immediately preceding them is 0.87 second. Average increase of *P-P* over preceding *PQP* is approximately 14 per cent.

An analysis of this table reveals a quantitative relationship between *QP* segment-lengths and subsequent *P-P* cycle-lengths. See text.

appears in cycles immediately following ventricular systole and for the fact that during longer periods of ventricular standstill, the slowing vanishes gradually over a succession of several cycles. This alone could account for the fact, furthermore, that the durations of *P-P* intervals are influenced and, in a measure, determined by the proximity of adjacent ventricular complexes.

The physiologic basis of an hypothesis which assumes that the mechanism underlying diastolic auricular slowing in heart block is an aortic-carotid sinus reflex is in keeping with known facts about the function of the cardiac vagus-sympathetic nerves and the mechanism of reflex cardiac inhibition. Normally, the tone of the vagus nerves is known to depend to a significant degree upon the pressure within the aorta and carotid arteries.[10] Increase of pressure within these vessels raises vagus tone, on the one hand, and, on the other, tends to lower the tone of its sympathetic antagonists. Decrease of pressure produces the opposite effect.[11,12] Reflex inhibition of the heart is a well-known phenomenon and the fact that striking alterations in vagal tone may occur as a result of single effective ventricular beats has been demonstrated clinically[7] and experimentally.[13] Based upon well-known properties of the cardiac vagus-sympathetic nerves and upon equally well-known hemodynamic events that accompany ventricular systole, the deduction that auricular irregularity in A-V heart block, as represented in the foregoing figures and tables, is the result of a vagus effect and that an aortic-carotid sinus reflex, initiated by ventricular systole, constitutes the underlying mechanism would seem reasonable.

It is realized, of course, that before such an hypothesis may be deemed valid, two conditions must be satisfied. First, since it assumes that auricular slowing in heart block is a function of vagus tone, it remains to be demonstrated that drugs which reduce vagus effect would tend to eliminate differences in cycle-lengths of *PQP* and *P-P* intervals. Second, since it assumes also that the vagus effect is initiated by a systolic rise in arterial pressure incident to ventricular systole, it remains to be demonstrated that ventricular systole is an essential component of the reflex mechanism and that slowing of the auricles does not appear in the wake of hemodynamically ineffective ventricular systoles.

To meet the first requirement, a case of complete heart block was observed under the influence of atropine. The drug was administered intramuscularly (grain 1/50) and electrocardiograms were taken before and during its effects. In order to produce magnified and clearly defined P waves with sharp summits and thus facilitate measurements, graphs were taken with right arm-chest leads and the sensitivity of the instrument was increased to a 2 cm. deflection for a millivolt. The graphs are illustrated in Fig. 5 as: *A*, before atropine; *B*, three to five minutes after; and *C*, one-half hour after atropine. As indicated in their legends, the graphs in these figures are sections of corresponding electrocardiograms containing 34, 35, and 33 consecutive auricular cycles, respectively, whose measurements are detailed in Table V *A*, *B*, and *C*.

The electrocardiogram taken *before atropine*, illustrated in Fig. 5,*A*, presents features already discussed for this type of graph. The durations of *P-P* intervals, for example, exceed those of *PQP* intervals preceding them and the longer *P-P*

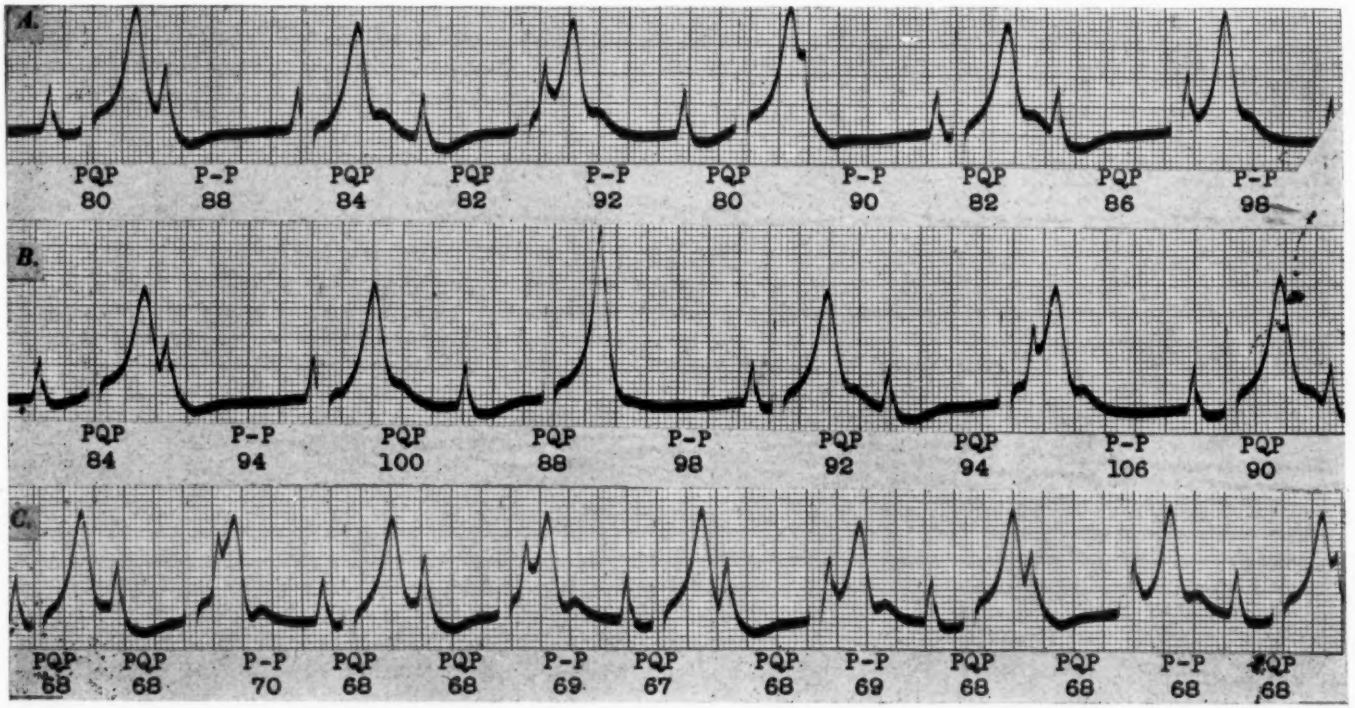

Fig. 5.—Effect of atropine on auricular irregularity in A-V heart block. Chest Lead CR_4; deflection 2.0 centimeters. Descending limb of QRS not illustrated. Unit of measure, 0.01 second.

A, before atropine. Ventricular intervals, 1.46 to 1.48 seconds. QRS-T, 0.50 second. Auricular intervals variable. As illustrated in Cycles 2, 5, 7, and 10, *P-P* cycle-lengths are related to *QP* segment-lengths. (Graph corresponds to Cycles 10 to 19 in Column *A* of Table V.)

B, three to five minutes after atropine. Ventricular intervals and QRS-T, approximately the same as in *A*. Auricular intervals are longer and highly variable (0.84 to 1.06 seconds). Note increase of *P-P* cycle-lengths as *QP* segment-lengths decrease. In Cycle 2 where initial P is on downstroke of T, *P-P* = 0.94 seconds. In Cycle 5 where initial P is at peak of T wave, *P-P* = 0.98 second. In Cycle 8 where initial P is on upstroke of T, *P-P* = 1.06 second. (Graph corresponds to Cycles 6 to 14 in Column *B* of Table V.)

C, one-half hour after atropine. Ventricular intervals, 1.08 seconds. QRS-T, 0.46 second. Range of auricular cycle-lengths, 0.67 to 0.70 second. For the most part, variations do not exceed 0.01 second. (Graph corresponds to Cycles 15 to 27 in Column *C* of Table V.)

intervals appear in the wake of comparatively short *QP* segments. As compiled from Table V,*A*, the average duration of first *P-P* intervals is approximately 0.93 second and the average duration of *PQP* intervals preceding them is 0.83 second. The increase of the former over the latter is approximately 11.5 per cent.

Graphs taken *three to five minutes after atropine*, illustrated in Fig. 5,*B*, manifest the initial, transient, vagotropic effect of the drug. The auricles are slower and the range of their cycle-lengths are greater. The three *P-P* intervals illustrated, namely, Cycles 2, 5, and 8, measure successively 0.94, 0.98, and 1.06 seconds, and, as shown in Table V,*B*, the *QP* segments within the *PQP* intervals preceding them are 0.46, 0.32, and 0.14 second, respectively. The progressive increase in *P-P* cycle-length which accompanies the gradual decrease in *QP* segment-length is strikingly illustrated in this figure. The inverse time relationship between *P-P* cycle-length and *QP* segment-length stands out conspicuously throughout Table V,*B*. The durations of *P-P* intervals vary, for example, between 0.94 and 1.06 seconds, their average being approximately 1.00 second. All *P-P* intervals which have cycle-lengths equal to or exceeding this average are preceded by short *QP* segments, 0.18 second or less.

At this point, attention is called to the third auricular interval in Fig. 5,*B*, which corresponds to Cycle 8 in Table V,*B*. Although this is a *PQP*, its duration, 1.00 second, not only exceeds all other *PQP* intervals but is, in fact, equal to the average duration of the *P-P* intervals in the table. This is the "exception to the rule" of which much has been made in some of the literature. If viewed, however, in the light of a reflex vagus effect, conditioned by the point of incidence of ventricular systole, this exception is understandable. Since in this *PQP* the initial ventricular complex is very close to the first P wave (P.Q.....P), there is adequate time for the operation of a relatively effective reflex which, because of this element of time and the increased sensitivity of the reflex mechanism as a result of the initial vagotropic effect of atropine, can appreciably delay the second P wave of the interval.

About *one-half hour after atropine*, an auricular rate of 88 a minute was attained. As illustrated in Fig. 5*C* and recorded in Table V*C*, even this limited vagoparalytic effect of the drug practically eliminated the differences between *PQP* and *P-P* cycle-lengths. According to the table, the average *PQP* measures 0.675 second while the average duration of *P-P* intervals is 0.687 second. The difference, approximately 0.01 second, is well within the range of error of computation. Although there are a few instances in the table where *P-P* exceeds *PQP* by 0.02 second, there are long periods where the durations of the two are identical (Cycles 24 to 33 in Table V *C*).

The illustrations in Fig. 5 and the measurements listed in Table V amply demonstrate that the vagoparalytic effect of atropine, although only moderate in this case, tends, nevertheless, to eliminate the auricular irregularity manifested by differences in *P-P* and *PQP* cycle-lengths in A-V heart block. Consequently, the observation supports the view that vagus tone is a factor in producing the irregularity and satisfies one of the requirments set forth as es-

TABLE V. MEASUREMENTS OF THREE CONSECUTIVE ELECTROCARDIOGRAMS IN A CASE OF COMPLETE A-V HEART BLOCK TO DEMONSTRATE THE EFFECTS OF ATROPINE ON THE AURICULAR RHYTHM. CYCLES IN BRACKETS ARE ILLUSTRATED IN CORRESPONDING FIGS. 5 *A*, *B*, AND *C*.

TABLE V. MEASUREMENTS OF THREE CONSECUTIVE ELECTROCARDIOGRAMS IN A CASE OF COMPLETE A-V HEART BLOCK TO DEMONSTRATE THE EFFECTS OF ATROPINE ON THE AURICULAR RHYTHM. CYCLES IN BRACKETS ARE ILLUSTRATED IN CORRESPONDING FIGS. 5 *A*, *B*, AND *C*.

NO.	A: BEFORE ATROPINE					NO.	B: THREE TO FIVE MINUTES AFTER					NO.	C: HALF-HOUR AFTER				
	PQ	QP	PQP	P-P	% INCR.		PQ	QP	PQP	P-P	% INCR.		PQ	QP	PQP	P-P	% INCR.
1	68	14	82			1	54	30	84			1	42	24	66		
2				94	14.63	2				98	16.67	2				67	1.52
3	36	44	80			3	20	64	84			3	10	57	67		
4				92	15.00	4	86	8	94			4	44	23	67		
5	12	68	80			5				104	10.64	5				68	1.49
6	76	8	84			6	38	46	84			6	12	56	68		
7				86	2.38	7				94	11.90	7	46	20	66		
8	54	26	80			8	8	92	100			8				68	3.03
9				92	15.00	9	56	32	88			9	12	56	68		
10	25	54	80			10				98	11.36	10	46	22	68		
11				88	10.00	11	18	74	92			11				70	2.94
12	6	78	84			12	80	14	94			12	14	54	68		
13	70	12	82			13				106	12.77	13	48	20	68		
14				92	12.20	14	26	64	90			14				69	1.47
15	38	42	80			15	84	12	96			15	12	56	68		
16				90	12.50	16				106	10.42	16	52	16	68		
17	14	68	82			17	30	58	88			17				70	2.94
18	80	6	86			18	90	8	98			18	18	50	68		
19				98	13.95	19				104	6.12	19	56	12	68		
20	44	40	84			20	38	48	86			20				69	1.47
21				94	11.90	21	96					21	22	45	67		
22	12	76	88			22		100				22	60	8	68		
23	74	16	90			23	50	38	88			23				69	1.47
24				98	8.88	24				96	9.09	24	26	42	68		
25	34	50	84			25	14	74	88			25	62	6	68		
26	94					26	80	10	90			26				68	0.00
27		94				27				100	11.11	27	28	40	68		
28	60	26	86			28	32	54	86			28	64	4	68		
29				94	9.30	29	94					29				69	1.47
30	20	62	82			30		104				30	28	40	68		
31	90					31	44	44	88			31	68				
32		92				32				96	9.09	32		68			
33	50	32	82			33	48	42	90			33	32	36	68		
34				92	12.20	34	70	18	88								
						35				100	13.64						

A, range of auricular cycle-lengths, 0.80 to 0.98 second. Average duration of *P-P*, 0.93 second; of *PQP* preceding them, 0.83 second.

B, range of auricular cycle-lengths, 0.84 to 1.06 seconds. Average duration of *P-P*, 1.00 second; of preceding *PQP*, 0.90 second. All *P-P* intervals of 1.00 second or over are preceded by *QP* segments of 0.18 second or less.

C, range of auricular cycle-lengths, 0.67 to 0.70 second. Average duration of *P-P* intervals, 0.687 second; of preceding *PQP*, 0.675 second. Note uniformity of Cycles 24 to 33 where nine out of ten cycle-lengths = 0.68 second.

sential to the validity of an hypothesis which holds that an aortic-carotid sinus reflex is the underlying physiologic mechanism of the auricular irregularity which accompanies A-V heart block.

It will be recalled in this connection that still another condition was to be satisfied. Since it has been assumed that the reflex mechanism is initiated by a systolic rise in arterial pressure incident to ventricular systole, it was to be demonstrated that a hemodynamically effective ventricular systole is an essential component of the reflex mechanism. Actually, observations presented so far lend considerable support in this direction. Ventricular systole has been repeatedly implicated as a factor in determining the degree of pacemaker inhibition. This has been amply demonstrated by the analysis of subgroups in Table IV and confirmed by Fig. 5,*B* and Table V,*B* which illustrate the vagotropic effects of atropine.

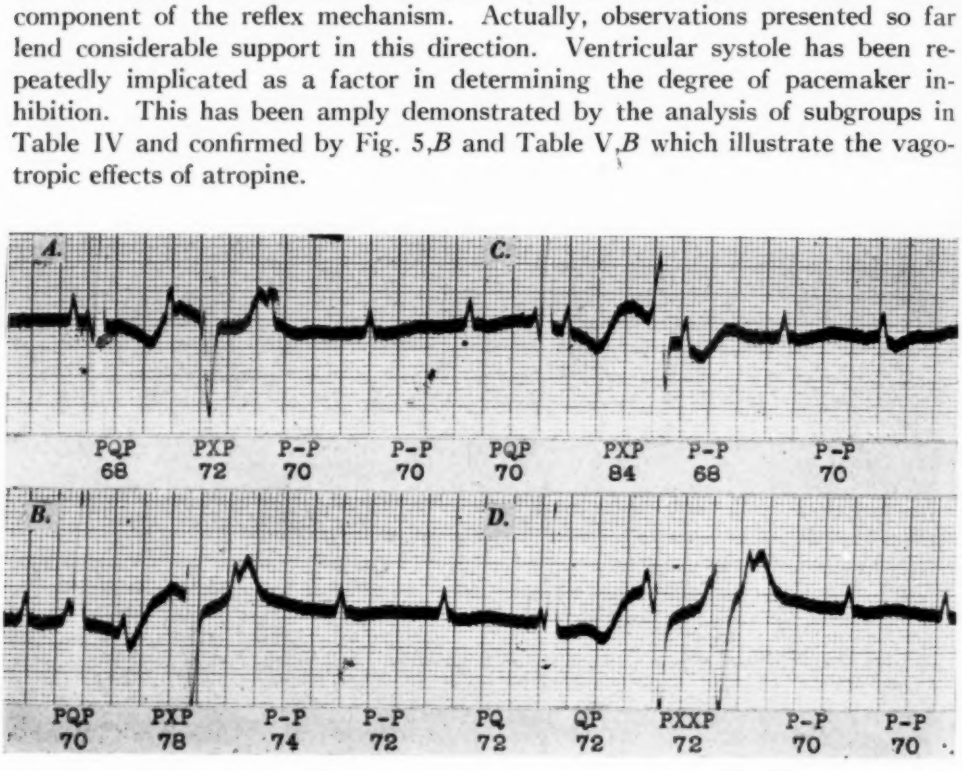

Fig. 6.—The gradual decrease, through Sections *A*, *B*, and *C*, of segments Q to P_1 is accompanied by a proportional increase in the duration of postsystolic auricular intervals, *PXP*. Although there is a similar decrease of segments X to P_2, the durations of postextrasystolic intervals *P-P* are not appreciably affected. In Section *D*, the segment Q to P_1 being very long, the duration of *PXP* is not altered. The next interval *P-P*, although in the wake of two extrasystoles, is also unaffected.

It is reasonable to assume that ventricular systole initiates the reflex vagus mechanism by way of a hemodynamic impulse. The large stroke volume which follows prolonged diastoles in A-V heart block can effectively stimulate the carotid sinus and aortic depressor nerves and thus set in motion the reflex which leads to inhibition of the auricular pacemaker. In order to demonstrate the role of this hemodynamic factor as the vis a tergo which provokes the reflex mechanism, a case of complete A-V heart block acccompanied by transient bigeminal and trigeminal rhythms due to ventricular premature beats was studied with a view to determining the relative effects of normal and premature ventricular

systoles upon auricular intervals which follow in their wake. This case affords an opportunity for a parallel study of the relative inhibitory effects of two types of ventricular systoles in the same subject.

As illustrated in Fig. 6 and detailed in Table VI, normal ventricular systoles in this case influence the durations of auricular intervals which follow in their wake in accordance with a rule already stated and repeatedly exemplified. The duration of these postsystolic auricular intervals, *PXP* (so designated because they contain an extrasystole), varies inversely with the duration of *QP* segments preceding them. In the four groups of complexes illustrated, *A*, *B*, *C*, and *D*, each beginning with a *PQP* interval, these variations in *QP* segment-lengths and *PXP* cycle-lengths, as well as in the percentage increase of postsystolic *PXP* over systolic *PQP* intervals, are striking. It will be noted, however, that although the durations of first postsystolic auricular intervals, *PXP*, are clearly influenced by the duration of the QP segments of normal ventricular systoles preceding them, second auricular intervals, *P-P*, which follow in the wake of extrasystoles, single or coupled, are not similarly affected. The time, *XP*, which elapses between the initial deflection of the premature ventricular systole and the initial P wave of the auricular interval which follows does not influence the duration of that interval. This holds true, in this case, no matter what the duration of the *XP* segment, and no matter what degree of inhibition the preceding normal systole had produced.

TABLE VI. MEASUREMENTS IN SECTIONS A, B, C, AND D OF A COMPLETE A-V HEART BLOCK WITH BIGEMINAL AND TRIGEMINAL RHYTHMS TO DEMONSTRATE THE RELATIVE INHIBITORY EFFECTS OF NORMAL AND PREMATURE VENTRICULAR SYSTOLES UPON THE AURICULAR PACEMAKER. UNIT OF MEASURE, 0 01 SECOND

SECTION	NO.	PQ	QP	PQP	PX	XP	PXP	% INCR.	P-P
A	1	14	54	68					
	2				24	48	72	5.88	
	3								70
	4								70
B	1	30	40	70					
	2				46	32	78	11.43	
	3								74
	4								72
C	1	48	22	70					
	2				60	24	84	20.00	
	3								68
	4								70
D	1	72?							
	2		72?						
	3				8	64	72	0.00	
	4								70
	5								70

PX and *XP* are component segments of auricular intervals *PXP* which follow in the wake of normal systole. *P-P* intervals, first and second, are those that follow in the wake of premature systoles.

In Section *D*, *PQ* and *QP* represent two whole auricular intervals. The P wave, terminal to the first and initial to the second interval, is obliterated by the QRS (see Fig. 6).

In each section, compare relative duration of *QP* and *PXP* with those of *XP* and *P-P*.

The marked contrast in the inhibitory effects of two different types of ventricular systoles in the same subject clearly indicates that an effective hemodynamic impulse is an essential component of the reflex vagus mechanism in A-V heart block. For, as has been demonstrated, when ventricular systole is normal and stroke volume seemingly adequate, *QP* segments are selective and when optimal, are followed by conspicuous slowing of the auricles. In the case of extrasystoles, on the other hand, there is no optimal *XP* segment for the obvious reason that extrasystoles, when hemodynamically ineffectual, lack the stroke volume necessary to provoke a reflex inhibition of the auricular pacemaker. These observations satisfy the second condition set forth as essential to the validity of an hypothesis which holds that an aortic-carotid sinus reflex, initiated by a rise in pulse pressure incident to ventricular systole, is the physiologic mechanism of the auricular irregularity which accompanies auriculoventricular heart block.

In the final appraisal of such a mechanism, certain seeming inconsistencies in auricular response to ventricular systole must be taken into account. Why, for example, is auricular irregularity conspicuous in some but only slight or even negligible in other cases of A-V heart block? Why is a short *QP* segment in the electrocardiogram of one subject an optimal condition for maximal postsystolic auricular slowing, while a longer *QP* range is optimal for another subject? Answers to these questions are implicit in the hypothesis of a reflex vagus mechanism, the properties of which are inherent in and peculiar to individuals. Clearly such properties of a reflex as its intensity, its latent period, or both, are themselves conditioned by certain intrinsic and extrinsic factors, apart from the initial force which provokes the reflex. In terms of an aortic-carotid sinus reflex, for example, the following may be regarded as intrinsic factors for a given subject: age, resiliency of arteries, blood pressure, and pulse rate; sensitivity of the aortic and carotid sinus receptor nerves, the vagus center, the vagus nerve and its myoneural junctions; and the nutritional state and the anatomic and physiologic integrity of the sinoauricular node. These, in the aggregate, determine the intensity and the latency of the reflex. There are other factors, more remote and extrinsic, whose effects on the vagus mechanism are transient and unpredictable. Pulmonary and gastrointestinal reflexes, pain, anxiety, and other emotional factors belong to this category.

In the realization, then, that a variety of intrinsic and extrinsic factors condition the properties of a vagus mechanism in a given subject, seeming inconsistencies regarded by some as mitigating against the concept of a reflex vagus effect upon the auricular pacemaker actually serve to support it. For only a mechanism subject to so many influences can account for the wide variations in the degree of auricular slowing encountered. Differences in reflex intensity, for example, would clearly account for the fact that not all cases of A-V heart block exhibit significant postsystolic slowing of the auricles. Differences in reflex latency, on the other hand, would explain why maximal slowing appears soon after ventricular systole in some, while in others, ventricular effect is considerably delayed. The electrocardiogram detailed in Table V, *B*, for example, where the computed optimal *QP* range is 0.08 to 0.18 second (average, 0.12

second) was recorded in the case of a 21-year-old man under the influence of the initial vagotropic effects of atropine. The electrocardiogram, the measurements of which are listed in Table II where the optimal *QP* segment range is 0.18 to 0.44 second (average, 0.30 second), was recorded in a 55-year-old man with arteriosclerotic heart disease. As the tables show, reflex intensity was high in both cases; reflex latency, on the other hand, was significantly different.

Any discussion of the latent period of a cardiac inhibitory reflex is beset with difficulties, not so much because of the complexity of the reflex arc but rather because the reflex involves a structure, the sinoauricular node, the physiology of which, as far as impulse production and impulse discharge are concerned, is not well known. Biologic processes, as a rule, are not linear but exponential functions. It is safe to assume, therefore, that for an effective inhibition of the auricular pacemaker the height of a reflex vagus effect would have to correspond to the early phase of impulse production. According to Ashman and Gouaux,[13] about 0.11 second elapses between the appearance of the initial ventricular complex in the electrocardiogram and the first evidence of the mechanical effects of ventricular systole upon the aortic and carotid sinus nerves. Since another 0.01 second is required for the completion of the reflex, these observations suggest that a reflex vagus effect on the sinoauricular node should appear approximately 0.12 second after the initial ventricular deflection. Kisch and Zucker,[14] in a study of a complete heart block in which there were evidences of sinoauricular block in the wake of ventricular systole, found a range of 0.13 to 0.39 second as optimal for the elimination of a sinus P wave. The variations in reflex response indicated in these reports correspond to our findings in the two cases cited. They are consistent with the mechanism of a reflex vagus effect, the behavior of which is conditioned by a variety of intrinsic and extrinsic factors peculiar to individual subjects.

SUMMARY

In auriculoventricular heart block, the rhythm of the auricles is often irregular. Illustrative electrocardiograms are presented to demonstrate patterns of this irregularity as they appear in partial and complete A-V heart block. The literature dealing with the mechanism of the auricular irregularity has been reviewed.

Measurements of large numbers of consecutive auricular intervals and their component segments in electrocardiograms of A-V heart block reveal that postsystolic slowing of the auricles is a characteristic feature of the arrhythmia and that the degree of slowing is essentially a function of the point of incidence of the initial ventricular deflection.

In the light of the knowledge that the tone of the vagus nerves depends, to a significant degree, upon the pressure within the aorta and carotid arteries, these observations have led us to regard the mechanism of auricular irregularity in A-V heart block as a reflex inhibition of the cardiac pacemaker initiated by a pressure rise within the aorta and carotid arteries, incident to the systolic injection of these vessels.

Observations on the auricular arrhythmia under the influence of atropine and observations on the relative inhibitory effects of normal and premature ventricular systoles in the same subject support this view. Seeming inconsistencies in auricular response to ventricular systole in A-V heart block are discussed in the light of the properties of a reflex vagus mechanism.

REFERENCES

1. Erlanger, J., and Blackman, J. R.: Further Studies in the Physiology of Heart Block in Mammals. Chronic Auriculo-Ventricular Heart Block in the Dog, Heart **1**:177, 1910.
2. Hecht, A. F.: Das Morgagni—Adams-Stokes Syndrome im Kindesaltern und seine Behandlung, Wien. med. Wchnschr. **64**:178, 1914.
3. Wilson, F. N., and Robinson, A. C.: I. Two cases of Complete Heart Block Showing Unusual Features, Arch. Int. Med. **21**:166, 1918.
4. Wenckebach, K. F., and Winterberg, H.: Die Unregelmässige Herztätigkeit, Leipzig, 1927, Wilhelm Engelmann.
5. Wolferth, C. C., and McMillan, T. M.: Observations on the Mechanism of Relatively Short Intervals in Ventriculo-Auricular and Auriculo-Ventricular Sequential Beats During High-Grade Heart Block, Am. Heart J. **4**:521, 1929.
6. Greybiel, A., and White, P. D.: Complete Auriculo-Ventricular Dissociation. A Clinical Study of Seventy-two Cases With a Note on a Curious Form of Auricular Arrhythmia Frequently Observed, Am. J. M. Sc. **192**:334, 1936.
7. Kisch, Bruno: Beobachtungen bei einem Kranken mit totalem Block, Cardiologia **2**:47, 1938.
8. Fatzer, Guy: Etude de l'electrocardiogramme dans le bloc atrioventriculaire, Cardiologia **10**:305, 1946.
9. Parsonnet, A. E., and Miller, R.: Heart Block. The Influence of Ventricular Systole Upon the Auricular Rhythm in Complete and Incomplete Heart Block, Am. Heart J. **27**:676, 1944.
10. Schweitzer, Alfred: Die Irradiation Autonomer Reflexe, Basel, 1937, S. Karger.
11. Von Brücke, E. T.: Zur Kenntinis des Reflexes von der Nasenschleimhaut auf die Herznerven, Ztschr. f. Biol. **67**:520, 1917.
12. Kisch, B., and Sakai, S.: Der Einfluss des Carotidenverschlusses auf die Herzfrequenz und auf die Wirkung peripherer Vagusreizung, Pflüger's Arch. f. d. ges. Physiol. **198**: 86, 1923.
13. Ashman, R., and Gouaux, J. L.: Reflex Inhibition of the Human Heart; A Complete A-V Block and Parasystole, Proc. Soc. Eper. Biol. & Med. **37**:25, 1937.
14. Kisch, B., and Zucker, G.: Sino-Auricular Block and Retrograde Auricular Conduction in a Case of Permanent Complete Heart Block, Am. Heart J. **23**:269, 1942.

EMBOLISM AT BIFURCATION OF AORTA

Review of Literature and Report of First Case Surviving After Gangrene

F. Stanley Morest, M.D.,* and Sidney Rubin, M.D.
Kansas City, Mo.

THROMBOSIS of the abdominal aorta was first described by Graham[1] in 1814. In 1898, when Welch[2] reviewed the literature, fifty-nine cases had been collected. Hesse[3] in 1921 collected seventy-three cases. These included forty-one of the cases mentioned by Welch. Wylde,[4] in 1922, reported two cases and, including his own, collected ninety-four cases. From 1922 to 1928, the following cases were reported: Aubertin,[5] two cases; Huesman,[6] one case; Lundblad,[7] two cases; Turreti and Guder,[8] one case; Somalo,[9] one case; Danisch,[10] one case; Menasci,[11] one case; and Tschervakoff,[12] one case. These cases were mentioned in the summary of the literature by Banowitch and Ira[13] in 1928 when they added five cases which they observed at Long Island College Hospital. In 1935 Rothstein[14] collected and reviewed briefly reports of thirteen cases of thrombosis and embolism of the abdominal aorta which occurred in infants and in children under 15 years of age. To these he added his own case. In the seven-year period following Rothstein's report, thirty-eight cases were recorded in the literature. In 1943 Greenfeld[15] reported five cases. When Santemma,[16] in 1946, reported two cases of aortic occlusion and theorized on the production of signs and symptoms, a summation of eight more cases had been added to the literature by individual case reports. Up to the present time, a total of 174 cases has been reported.

Another case of embolus at the bifurcation of the aorta is herewith presented because of its clinical variation from those already reported.

CASE REPORT

Mrs. A. P., Case No. 32363, a 47-year-old white woman, was admitted to Research Hospital on Jan. 22, 1947, fourteen days after an embolic episode. Approximately fourteen days before admission, there was a sudden attack of pain in the right chest, which was followed by expectoration of bright red sputum and fever. On the next day, the patient had sharp pain below left costal arch which lasted for six hours. Two days later, a sudden excruciating pain was experienced in both legs simultaneously. This pain was associated with tingling and numbness. Color change began soon after this painful episode, and the legs were described as being blue and cold. The degree of change progressed until the lower portion of the legs was black.

Received for publication Sept. 13, 1947.
*From Medical Service No. 3, Research Hospital, and Vascular Department, Research Clinic.

Physical Examination.—The temperature was 101° F.; pulse rate, about 72 per minute and irregular; respirations, 32; and blood pressure, approximately 98/60. No murmurs were audible at this time, and the cardiac sounds were of poor quality and distant. There was a total irregularity of heart rhythm with an apical rate of about 120 beats per minute, making a peripheral pulse deficit of approximately 50. Jugular vessels pulsated and were markedly engorged. The liver was palpable 2.0 cm. below the costal margin, and the spleen was tender.

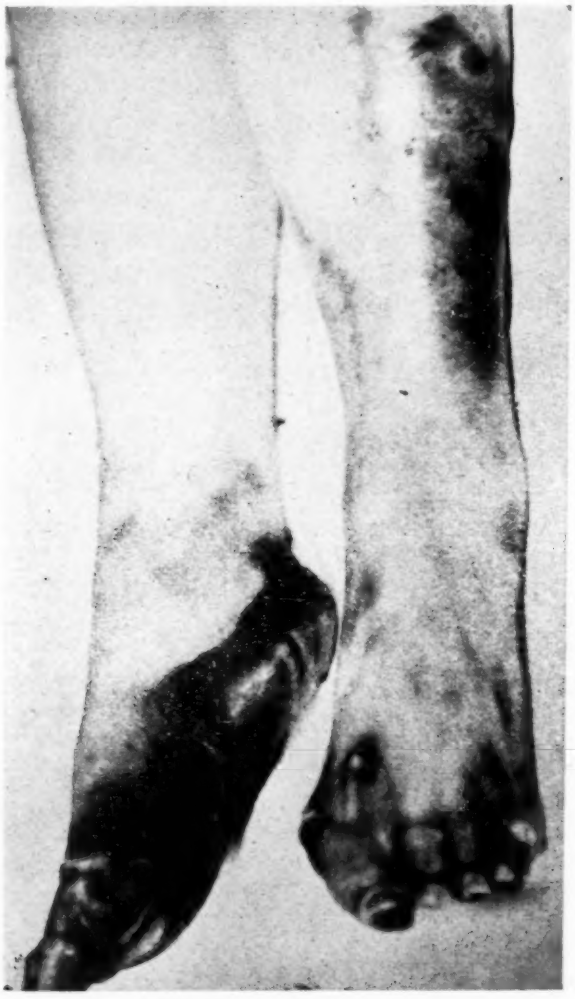

Fig. 1.—Extremities of Mrs. A. P., fourteen days after onset of gangrene from riding embolus.

The extremities presented the most dramatic findings. A symmetrical pattern of dry gangrene was present over the feet and legs, extending up to 17 cm. below the knees. Gangrene had destroyed the normal contours of the feet and digits to such a degree that the exact outline of the underlying bony framework was apparent through the overlying skin which was dry and black and drawn at the interphalangeal joint spaces. Necrosis extended up the leg, destroying tissue substance (Fig. 1). A hyperemic border of several millimeters surrounded the gan-

grenous area. The skin proximal to this area was of a normal appearance, and sensory modalities were intact. There was a slight degree of edema present which was demonstrated by pitting of the skin. Femoral pulsations were only faintly palpable, while the popliteal arteries could not be felt.

Laboratory Data.—The white blood cells were 19,600. Electrocardiographic tracing showed auricular fibrillation. A 2-meter roentgenogram of the chest at the time of admission revealed clear lung fields. There was, however, gross enlargement of the cardiac shadow in all its diameters, particularly the transverse, and a definite bulge along the middle third of the left heart border.

Diagnosis.—Our diagnosis was: (1) Rheumatic fever (inactive); (2) mitral stenosis; (3) hypertrophy of cardiac chambers (left and right auricles and right ventricle); (4) cardiac insufficiency (left and right ventricular); (5) auricular fibrillation; (6) functional capacity, Class IV (Classification E of American Heart Association classification). Additional diagnoses included: (1) Bilateral gangrene of feet, ankles, and lower halves of legs caused by a saddle embolus at bifurcation of aorta resulting from embolization from the left auricle; (2) recent pulmonary and splenic infarctions due to emboli from right and left auricles, respectively.

Clinical Course.—Several hours after admission, the patient began to chill. Chilling was severe and associated with generalized myoclonic movements. It was felt at this time that absorption of toxins from the necrotic tissue was the cause of this episode, and it was apparent that immediate action was necessary. Because of the cardiac status of the patient (there now were congestive râles in both lung bases), refrigeration was considered to be the treatment for prevention of further absorption of necrotic toxins as well as the best anesthetic in providing for the inevitable amputations. In addition, refrigeration would produce analgesia, obviating the necessity of repeated injections of opiates to relieve pain.

Ice was then placed about both extremities to the level of anticipated site of amputation. Use of ice produced a rapid "physiologic amputation" which allowed time for digitalizing the patient and for improvement in her general condition in preparation for surgical amputation.

Other than refrigeration, sedation was all that was necessary for sufficient anesthesia during surgical procedure. Both gangrenous extremities were amputated above the knees simultaneously by two surgical teams.* Rapid technique was considered essential in preventing shock.

Immediately postoperatively, penicillin and Dicumarol were started. There were no signs of shock, and the course was uneventful with penicillin and Dicumarol being discontinued on the seventh and fourteenth days, respectively. A transfusion of 500 c.c. of citrated bank blood restored the previously low cell count and hemoglobin to a normal level. At the time this paper is written, it has been four months since the patient left the hospital, and the stumps are healed. The patient carries on some of her household duties in a wheel chair. Orthopedic surgeons* are conditioning the stumps for artificial limbs in two months.

DISCUSSION

Cardiac thrombi which may cause aortic embolism are of two types: the smaller type, which arises from mycotic vegetations, usually on the mitral or aortic valves, associated with valvular endocarditis; and the larger type that is usually found where circulation is slowest, as in the auricular appendages and in the apices of the ventricles between the columnae carneae. Most frequent sources of arterial emboli in the systemic circulation are mural thrombi in the left auricle or left ventricle. These form in a fibrillating left auricle present in rheumatic or arteriosclerotic heart disease. In mitral stenosis, mural thrombi from an enlarged left auricle, especially when fibrillating, may send an embolus to lodge at the aortic bifurcation. In myocardial infarction having subendo-

*Harold V. Zuber, M.D., and Ralph E. Mueller, M.D.

cardial localization in the left ventricle, mural thrombi form and some may break loose to become arterial emboli. Mural thrombi also form in an enlarged left ventricle in cases of congestive failure resulting from hypertension or from coronary artery disease.

The portion of the abdominal aorta usually affected by an embolus is that below the origin of the mesenteric arteries. There are two types of emboli responsible for the syndrome of riding embolus, one of which completely occludes the lower end of the aorta and the other only incompletely occludes it. When either type of these emboli strikes the aortic bifurcation, terrific reflex angiospasm occurs instantly throughout the entire arterial system of both legs. In many instances, immediate occlusion of the lower end of the aorta results from intense localized spasm. Distal, soft, taillike secondary propagation thrombus formation starts in several hours and extends a variable distance into the iliac arteries. The farther the secondary thrombus formation extends down the iliacs and the longer the delay in treatment, the more collateral arteries are occluded. Secondary propagation thrombi usually extend farther down one iliac artery than down the other, so that variations in symptoms, prognosis, and treatment follow.

In the majority of the cases reported in the literature, the onset of symptoms has been acute. The patient is suddenly seized with a severe, sharp, intense, agonizing pain, referable in most instances to the lower extremities. Intense pain may not necessarily be present at the start, and in nearly half the cases numbness or paralysis points to a sudden occlusive arterial lesion. Tenderness or pain over distal propagation plugs occurs late. Backache is a special symptom to localize the lesion to the aortic bifurcation. Skin changes include pallor or mottled cyanosis, coldness of entire lower extremities below the level of adequate collaterals, collapsed veins, loss of sensation, diminished reflexes, and evidence of partial paralysis of one or both extremities.

Thus, this dramatic picture presents varied symptoms and signs, but early diagnosis and prompt treatment are possible if physicians think of this syndrome in types of heart disease mentioned and examine peripheral arterial pulsations routinely in such patients when making rounds.

Differential Diagnosis.—Sudden arterial occlusion of one extremity has been mistaken for embolism at the bifurcation of the aorta, but findings are always unilateral. Likewise, the clinician must be cognizant of the difference between single arterial occlusion with or without gangrene and saddle embolus with or without gangrene in which the propagation thrombus involves just one iliac artery. Here again findings are always unilateral in single arterial occlusive lesions, while in saddle embolus there are findings of coldness, pallor, and numbness in both extremities from the onset. Should gangrene later develop in one leg, confusion should not ensue because the other leg will not show any change from normal in a single arterial occlusive lesion but will exhibit findings in the case due to saddle embolus. A patient with venous obstruction has an extremity with normal or elevated skin temperature, distended veins, cyanosis, edema, and in which arterial pulsations can frequently be identified. Gangrene seen in the

patient with arteriosclerosis obliterans as a result of intravascular thrombosis is easily differentiated from the sudden and dramatic syndrome under discussion. Functional peripheral circulatory disturbances or thromboangiitis obliterans with its arterial insufficiency of the upper extremities also are not likely to be confused.

Treatment.—Treatment of saddle embolus is the same as that for sudden, single, peripheral arterial occlusion in general with special attention given to several points which apply to this entity specifically. Prophylactically, prevention is possible if Dicumarol is administered routinely in coronary occlusion when such patients are in a hospital where accurate determination of prothrombin time can be performed and there are no contraindications.

The principles for treatment of sudden arterial occlusion, as laid down by Allen, Barker, and Hines, Jr.,[17] are followed in the early stage which is the pregangrenous stage. There are three things *not* to do in these cases. First, do not elevate the extremities; second, do not apply heat; and third, do not delay treatment. An opiate is given as soon as the diagnosis is made; morphine sulfate, grain ¼ to ½, is administered, giving part of the solution intravenously and the balance subcutaneously. Then, papaverine hydrochloride is given intravenously in doses of 1 to 2 grains every four hours. The first dose may be injected into a femoral artery. This is to relax arterial spasm, which is further relieved by maintaining temperature of the room between 85° and 95° Fahrenheit. An ounce or two of whiskey is, in most instances, the best sedative as well as being a vasodilator. The patient should be placed on an oscillating bed. Heparin and Dicumarol are started as early as possible in all cases.

Failure to gain restoration of adequate circulation in a few hours calls for procaine sympathetic block. Should the circulation not be restored in about eight to twelve hours after onset of the embolic phenomenon and the carrying out of procedures described herein, embolectomy is performed under local or regional anesthesia. Since anticoagulant therapy has been used widely, circulation is restored more often and embolectomy required fewer times than formerly.

When gangrene is already present, bilateral amputation is the only course, anticoagulants being of no help at this late stage. Management of this late stage, which is the gangrenous stage, is presented so that life, not limbs, may be saved. Cardiac reserve must be evaluated and proper measures taken to restore it if necessary. Inadequate digitalization, if noted by signs of cardiac insufficiency, can be overcome carefully yet quickly with glycosides of digitalis since there may not be time enough to wait for the slow effects of whole leaf.

Physiologic amputation is performed quickly by placing the legs in ice to within four inches of the anticipated site of amputation. Place a tourniquet at this level. This treatment can be kept up for several days, if necessary, to get the patient into best possible shape for surgery. Four hours before surgery, apply ice at least four inches above amputation site, and apply the second tourniquet at this level. By this method tissue asphyxiation and a viable stump are obtained. Do not add salt because this produces freezing of tissue and results in necrosis of stump, necessitating secondary amputation.

Most often amputation below the knee is satisfactory in embolus at the bifurcation of the aorta.[18] Though the site of the embolus is higher, the level of amputation is lower than for most cases of single artery occlusion having the same extent of gangrene. This is because riding embolus occurs more often in middle-aged individuals who, as a rule, will have more general vitality, less arteriosclerosis, and better collateral circulation than elderly patients. As a result of all of these factors, the intima will be less likely to be damaged irreversibly by ischemia from angiospasm, whereas in the elderly patient, more extensive arterial thrombosis and poor collateral circulation will result in amputations being done more frequently above the knees.

Immediately postoperatively, Dicumarol is started to prevent venous thrombosis. This phase of treatment eliminates a common cause of postoperative death from amputation, namely, pulmonary embolism from thrombosis of a leg vein. Refrigeration prevents postoperative shock so that patients with poor cardiac reserve, like those in functional Classes III and IV (American Heart Association), can now survive. The possibility of morbidity or mortality from postoperative infection will usually be prevented by continuing the administration of penicillin for one week.

Prognosis.—The prognosis is always grave. Hesse[3] showed that 95 per cent of seventy-three patients died under conservative therapy. In the review by Rothstein,[14] it was brought out that 112, or 91 per cent, of the 123 patients reported up to 1935 expired. In the summary by Greenfield[15] in 1943, of a total of 161 patients, 147, or 91.3 per cent, succumbed. Death occurred from within several hours to three months after onset of symptoms. Mortality following gangrenous changes has been 100 per cent. The case reported herein falls into a different group, especially since the gangrene had been present for fourteen days prior to surgery. Aside from the duration of gangrene, our patient was, in addition, a very poor surgical risk (Class IV-E) as are all such individuals who have auricular fibrillation and myocardial insufficiency and who experience arterial embolism. As far as a review of the literature shows, this is the only patient to survive after extensive gangrene of such duration.

SUMMARY

1. Attention has been directed to a complete review of the literature concerning embolism at the bifurcation of the aorta.

2. Emboli occluding the abdominal aorta are of cardiac origin.

3. Symptoms of abdominal aortic obstruction may be slowly progressive or rapid in onset.

4. Sudden, single arterial embolic occlusion, arterial thrombosis of one extremity, and venous obstruction are differentiated from riding embolus.

5. Prophylaxis of saddle embolus is discussed, as well as treatment of the early and late stages.

6. A case of embolus at the bifurcation of the aorta is presented because of its clinical variation from those already reported, because refrigeration, utilized

for both therapy and anesthesia, altered a heretofore grave prognosis, and because our patient is the first one reported who survived after gangrene of such duration.

7. Mortality following gangrenous changes has been 100 per cent; but now, with refrigeration for both therapy and anesthesia, with anticoagulants, and with penicillin, these heretofore doomed patients can survive.

REFERENCES

1. Graham, R.: Case of Obstructed Aorta, Med. Chir. Trans., London, **5**:1 297, 1814.
2. Welch, H. W.: Embolism and Thrombosis. In Allbutt, C., and Rolleston, H. D.: System of Medicine, ed. 2, London, 1910, Macmillan & Company, Ltd.
3. Hesse, E.: Ueber die Embolie und Thrombose der Aorta Abdominalis und ihre Operative Behandlung, Deutsches Arch. f. klin. Chir. **15**:1812, 1921.
4. Wylde, C. O.: Embolism of Abdominal Aorta, Canad. M. A. J. **12**:647, 1922.
5. Aubertin, M.: Thrombosis of the Aorta, Ann. de méd., **10**:454, 1921.
6. Huesman, H.: Thrombose der Aorta und beider iliacae, München. med. Wchnschr. **70**: 396, 1923.
7. Lundblad, O.: Three Cases of Embolus, Two at Bifurcation of the Aorta, One in Common Iliac; Operation, Acta. chir. Scandinav. **57**:375, 1924.
8. Turreti, G., and Guder, R.: Un Cas d'Embolie Aortique D'Origine Mitrale, Operation, Rev. méd. de la Suisse Rom. **44**:739, 1924.
9. Somalo, M.: Consideraciones Sobre un Caso de Embolia de la Bifurcacion de la Aorta, Semana med. **32**:1050, 1925.
10. Danisch, F.: Hemorrhagic Infarction of the Uterus and Adnexa by Thrombosis of the Abdominal Aorta and Pelvic Arteries, Centrabl. fur Gynak. **50**:1234, 1926.
11. Menasci, R.: Aortic Thrombosis Complicating Influenza, La Riforma Med. Naples, **43**: 149, 1927.
12. Tschervakoff, V. F.: Obturational Thrombosis of Abdominal Aortae, Russk. Klin. **7**:860, 1927.
13. Banowitch, M. M., and Ira, G. H.: Embolism and Thrombosis of the Abdominal Aorta, M. Clin. North America **11**:973, 1928.
14. Rothstein, J. I.: Embolism and Thrombosis of Abdominal Aorta in Infancy and Childhood, Am. J. Dis. Child. **49**:1578, 1935.
15. Greenfield, I.: Thrombosis and Embolism of Abdominal Aorta, Ann. Int. Med. **19**:656, 1943.
16. Santemma, E. E.: Occlusion of Aortic Bifurcation With Theoretic Consideration Regarding Production of Signs and Symptoms in 2 Cases, New York State J. Med. **46**:416, 1946.
17. Allen, E. V., Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, Philadelphia, 1946, W. B. Saunders Company, p. 325.
18. Allen, Edgar V.: Personal communication.

ELECTROCARDIOGRAPHIC CHANGES IN TYPHOID FEVER AND THEIR REVERSIBILITY FOLLOWING NIACIN TREATMENT

M. RACHMILEWITZ, M.D., AND K. BRAUN, M.D.*
JERUSALEM, PALESTINE

ANY infectious disease may affect the heart and the circulatory system. The cardiac involvement may be so severe as to produce marked clinical manifestations and even heart failure and death. In such cases, pathologic examination reveals profound changes, manifested either by toxic parenchymatous degeneration or by actual myocarditis, that is, inflammatory infiltration of the heart muscle. Chief among the infectious diseases severely affecting the heart are rheumatic fever, diphtheria, and syphilis. The cardiac involvement in these diseases is evidenced by clinical manifestations and by abnormalities in the various phases of the electrocardiogram. In recent years electrocardiographic alterations have been described in various acute infections not directly affecting the heart, such as pneumococcus pneumonia,[1] infectious hepatitis,[2] mumps,[3] and infectious mononucleosis.[4] These electrocardiographic changes are transient and disappear after recovery.

Of the infectious diseases rarely affecting the heart anatomically, typhoid fever has been the subject of a number of electrocardiographic studies. Most of these investigations were reported in the European literature. Clerc and Levy[5] examined the electrocardiograms of ten cases of typhoid fever, in five of which electrocardiographic changes were found. The alterations consisted of diphasic or negative T waves, especially in Lead II. Arieff and Tigi[6] found a high incidence of electrocardiographic alterations in a series of thirty-five cases of typhoid fever. The abnormalities consisted of prolongation of the P-R interval in eighteen cases and flattening of the T waves in the remaining seventeen cases. According to these authors the changes usually appear during the acme, and occasionally, one to two weeks after defervescence. Chagas[7] described electrocardiographic changes in six cases of typhoid fever. In two of them, disturbances in the rhythm were found, in one there was total, and later partial, auriculoventricular block, and in the three remaining cases T-wave changes were noted. Bucham and Daniels[8] observed changes of the T waves, which were negative, flat, diphasic, or isoelectric in five out of nineteen cases of typhoid and paratyphoid fever. No data were recorded regarding the duration of the T-wave abnormalities. Lukomski[9] observed the following changes in a series of sixty cases of typhoid fever: prolonga-

From the Department of Internal Medicine (Div. B.), Rothschild Hadassah University Hospital, Jerusalem, Palestine.
Received for publication Sept. 17, 1947.
*Present address: The Michael Reese Hospital, Chicago, Ill.

tion of the P-R interval in 33 per cent and S-T and T-wave abnormalities in about 30 per cent, but this also included cases with negative T waves in Lead III only. The T-wave changes generally appeared at the height of the temperature and persisted after defervescence, disappearing only several weeks after recovery. Gurewitsch[10] examined sixty-five children suffering from typhoid fever. In twenty-four cases pathologic changes in the electrocardiogram were found; these consisted of flattening of all the deflections, especially of the T waves. These changes were sometimes observed even as late as six months after recovery. This author stressed the fact that the severity of the typhoid infection bore no relationship to the presence of electrocardiographic abnormalities. Giraud-Costa and Raybaud[11] recently summarized their electrocardiographic findings in 510 cases of typhoid fever studied since 1933. The most frequent changes in the electrocardiogram were alterations of the T waves, which were flat, diphasic, or inverted. Prolongation of the P-R interval was also observed in a number of cases. Other disturbances in conduction and arrhythmias were rare. The changes in the electrocardiogram appeared at the height of the disease and continued into the convalescent period. According to these authors, the patient enters and leaves the hospital with a normal electrocardiogram.

Reports on this subject in the American literature are scarce. Brow[12] reported electrocardiographic findings in sixty-five cases of typhoid fever, in 21.5 per cent of which prolongation of the P-R interval was found. Only two cases showed T-wave changes. The earliest change appeared on the second day, and the latest on the forty-third day. No clinical signs of cardiac involvement were present in the entire group. Porter and Bloom[13] examined thirty cases of typhoid fever, in fourteen of which significant changes in the electrocardiogram appeared between the ninth and the forty-fourth day. In nine of these cases, prolongation of the P-R interval was observed, while alterations of the T waves were seen in only four cases. These changes lasted longer than six days in only two instances. From a clinical point of view there were no abnormal manifestations of the cardiovascular system. Stuart and Pullen,[14] in a recent clinical study of 360 cases of typhoid fever in New Orleans, found one case with prolongation of the P-R interval and five cases with T-wave changes among sixteen cases examined electrocardiographically.

Our observations are based upon electrocardiographic studies on fifty cases of typhoid fever treated during the past three years. With a single exception, all were without clinical evidence of previous heart disease. There were no fatalities in this series of cases; in the majority the course was of moderate severity. No serious complications were encountered except for intestinal hemorrhage in two cases, and agranulocytosis in one. Fifteen cases in which repeated chills, a high degree of toxemia, or continued diarrhea appeared during the course of the disease received sulfa drugs or penicillin as long as these manifestations lasted. Otherwise, small doses of antipyretics and sedatives were prescribed. The diet during the febrile period consisted of 240 Gm. of carbohydrates, 90 Gm. of fat, and 75 Gm. of proteins given in liquid or semiliquid form. Serial electrocardiographic examinations were made upon admission to the hospital and at frequent intervals during the course of the disease and the convalescent period. Standard limb leads

and precordial Lead IVF were recorded. Each recording was made with the patient in the recumbent position. In addition, the routine cardiovascular examinations were performed, special attention being paid to the appearance of heart murmurs and myocardial insufficiency.

RESULTS

Among the total of fifty cases, fifteen showed no electrocardiographic changes on repeated examinations during the entire period of observation. This group included four cases in which the typhoid infection was severe. The average duration of the febrile period in this group was twenty-six and one-half days. Electrocardiographic alterations were found in a group of thirty-five cases with an average febrile period of twenty-eight days. The age incidence in this group did not differ significantly from that of the other group with abnormal electrocardiographic findings. A description of these changes follows.

P-R Interval.—Only three cases showed a prolonged P-R interval (0.24, 0.25, and 0.28 second, respectively). These changes appeared during the febrile period. In one case the P-R interval remained prolonged for only six days and became normal while fever was still present. In the other two cases the prolonged P-R interval persisted into convalescence.

P Wave.—P waves showed no significant deviations from the normal.

QRS Complex.—In two cases there was a decrease in the voltage of the QRS complex during the febrile period. The voltage returned to normal during convalescence.

Q-T Interval.—This was calculated by Bazett's formula: $QT = K\sqrt{R\text{-}R}$, where K is a constant. The average value for K in normal men is 0.374, and in normal women, 0.383.[15] There was no significant deviation from these values during the disease or after recovery.

RS-T Segment.—Changes in the RS-T segment were not significant. In only four cases was there a deviation of 1.0 mm. or less from the base line.

T Wave.—The most conspicious changes were found in the T waves. All thirty-five cases showed some degree of abnormality in the T waves, which were of low amplitude (less than 2.0 mm.), isoelectric, or diphasic. The following (Table I) gives an account of the frequency of T-wave changes in various leads.

TABLE I.

T-wave changes in all leads	24
T-wave changes in Leads I, II, and IVF	1
T-wave changes in Leads II, III, and IVF	2
T-wave changes in Leads I and IVF	2
T-wave changes in Leads I and II	4
T-wave changes in either Lead I or Lead II	2
Total	35

The course of the T-wave alterations was followed throughout the disease. As soon as the T waves became flatter, electrocardiograms were taken frequently to record the successive changes. The abnormalties of the T waves appeared in twenty-eight cases after defervescence, in two cases during the febrile period, and in the remaining five cases in the decrescent phase of the febrile period. There was no relationship between the severity of the disease and the degree of the electrocardiographic abnormalities, nor did the duration of the disease or the presence of complications have any apparent bearing on the severity of the electrocardiographic alterations. No clinical cardiovascular disturbances or subjective complaints referable to the heart were noted in the patients showing marked electrocardiographic changes.

THE EFFECT OF NIACIN UPON THE ELECTROCARDIOGRAPHIC CHANGES

Since in the majority of patients the T-wave alterations appeared simultaneously with clinical signs of vitamin B deficiency and since the electrocardiographic changes resembled those seen by us in niacin deficiency,[16] twenty-three patients were given niacin. Daily doses of 300 to 600 mg. of niacin were given orally and in some cases also intravenously. This treatment was begun after the electrocardiographic alterations had become pronounced and constant. In all

TABLE II. ELECTROCARDIOGRAPHIC FINDINGS

CASE NO.	SEX	AGE	BEFORE TREATMENT	AFTER TREATMENT WITH NIACIN
1	M	35	T_1, T_4 flat,* T_2, T_3 isoel. S-T_2, S-T_3 depressed	T_1++, T_2+++, T_4+++ S-T_3 isoel.
2	M	17	T_1, T_4 flat, T_2 isoel.	T_1++, T_2++, T_4+++
3	M	16	T_1, T_2, T_4 flat	T_1++, T_2++, T_4+++
4	F	47	T_1, T_2 flat	T_1++, T_2+
5	F	18	T_1, T_2, T_4 flat S-T_1 depressed,	T_1++, T_2+, T_4++ S-T_1 isoel.
6	F	47	T_1, T_4 diphas., T_2, T_3 isoel.	T_1++, T_2+, T_4++
7	F	31	T_1, T_2, T_4 flat	T_1++, T_2+, T_4++
8	F	30	T_1, T_4 flat, T_2 isoel.	T_1++, T_2++, T_4++
9	F	45	T_1 flat, T_2, T_4 isoel.	T_1++, T_2++, T_4++
10	F	25	T_1 flat, T_2, T_3, T_4 isoel.	T_1+++, T_2++, T_4+++
11	M	24	Low voltage of QRS T_1, T_4 flat	T_1++, T_4+++
12	M	25	T_1, T_2, T_3, T_4 isoel.	T_1++, T_2++, T_4+++
13	F	24	T_1, T_2, T_4 flat	T_1++, T_2+, T_4+++
14	F	29	T_1, T_2 flat, T_4 isoel.	T_1+, T_2+
15	M	19	T_1, T_2, T_3 flat S-T_2, S-T_3 depressed	T_1++, T_2++ S-T_2, S-T_3 isoel.
16	F	42	Low voltage of QRS T_1, T_2 flat, T_4 isoel.	T_1++, T_2++
17	M	30	T_1 isoel., T_2, T_3, T_4 flat	T_1+, T_2++, T_3+, T_4+++
18	F	28	T_1, T_4 flat, T_3 isoel.	T_1+, T_2++, T_4++
19	M	32	T_1, T_2, T_4 flat	T_1+, T_2+, T_4++
20	M	32	T_1, T_3 isoel., T_2, T_3 flat	T_1+, T_2++, T_3+
21	F	32	T_1, T_4 isoel., T_3 isoel.	T_1+, T_2+, T_3+
22	M	45	T_1, T_2, T_3 flat, T_4 isoel.	T_1+++, T_2+++, T_4++
23	M	23	T_1, T_2, T_4 flat	T_1++, T_2+++, T_4+++

*The term "flat" is used to signify a voltage of less than 2 millimeters.

cases there was marked improvement in the electrocardiogram following this treatment. The return of the electrocardiogram to normal was observed after short periods of niacin medication: in six cases, after two days; in twelve cases, after three to five days; and in four cases, after six to ten days. Table II presents the electrocardiographic findings before and after treatment. The degree of elevation of the T waves was designated as Plus 1 (+), corresponding to an elevation of 0.5 mm. +0.25 mm.; as Plus 2 (++), corresponding to an elevation of 1.0 mm. +0.25 mm.; and as Plus 3 (+++), corresponding to an elevation of 1.5 mm. and more.

The following case histories illustrate the development of the electrocardiographic changes in typhoid fever and the effect of niacin treatment on these changes.

CASE 1.—R. E., a 30-year-old woman, was admitted on Nov. 1, 1945, with a history of general malaise, headache, anorexia, and fever of a fortnight's duration. The fever started with a chill which was followed by a sudden rise of temperature to 41° centigrade. The pyrexia persisted, ranging between 38° C. in the morning and 41° C. in the evening.

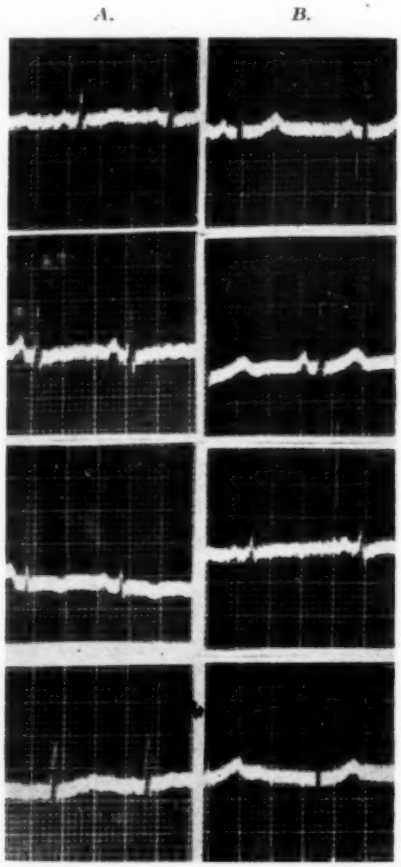

Fig. 1.—*A*, Electrocardiogram taken during convalescence: T_1, T_2 isoelectric, T_4 diphasic. *B*, After two days' treatment with niacin, the electrocardiogram is normal.

On admission, the patient appeared severely ill, the tongue was coated, and the spleen was palpable 2.0 cm. below the left costal margin. Neurological examination revealed rigidity of the neck, a hyperactive right patellar reflex, and increased skin sensitivity to pain in both legs. The Kernig sign was negative. The white blood cells were 5,000, with 56 per cent neutrophiles, 30 per cent lymphocytes, 6 per cent monocytes, and 8 per cent band-form neutrophiles. Cerebrospinal fluid after lumbar puncture gave a positive Pandy reaction and a normal cell count. Eight days after admission rose spots were seen, and the Widal agglutination test, which had been negative on admission, became positive.

On November 16, thirty-one days after the onset of the disease, the temperature became normal and the patient made an uneventful recovery. During the convalescent period she complained of a burning sensation in the tongue which was bright red and showed atrophy of the papillae.

Serial electrocardiograms were made during the patient's stay in the hospital. Three normal tracings were recorded during the febrile period. After the fall in temperature, the T wave became flat and the electrocardiogram became definitely abnormal. Two electrocardiograms on November 20 and November 25 showed the same alterations: T_1 and T_2 isoelectric, T_3 inverted, and T_4 diphasic (Fig. 1,*A*). On November 25, treatment with niacin, 600 mg. daily, was commenced. After two days of treatment, a marked elevation of the T waves was noted and the record became normal (Fig. 1,*B*).

Niacin excretion in the urine during the course of the disease was examined in this case. A continuous and gradual decrease was observed; from 5.5 mg. per liter at the height of the

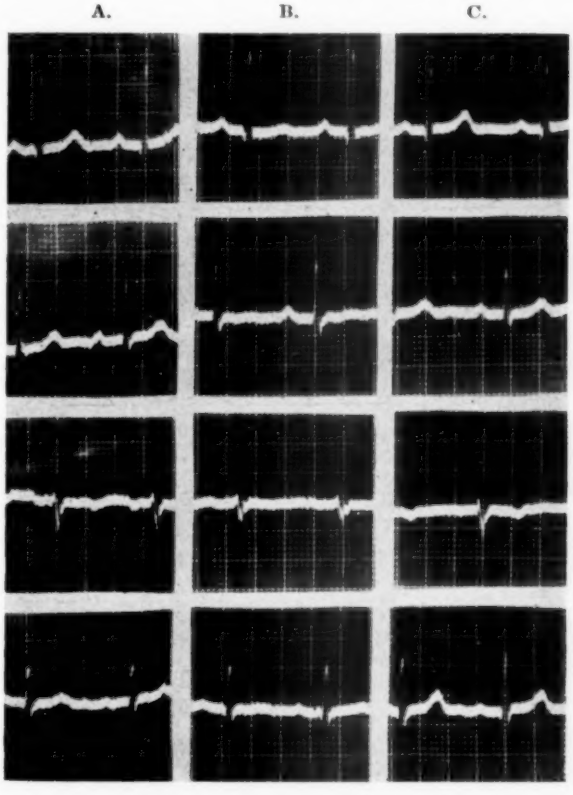

Fig. 2.—*A*, Normal electrocardiogram taken during the febrile period. *B*, Electrocardiogram taken after defervescence: T_1 flat, T_2, T_3, and T_4 isoelectric. *C*, After two days of treatment with niacin the tracing became normal.

disease to 0.60 mg. per liter at the time of convalescence. The lowest values of niacin were obtained at a time when electrocardiographic alterations were most pronounced.

CASE 2.—T. S., a 25-year-old woman, was admitted on Sept. 4, 1945, complaining of fever of a fortnight's duration. The disease had started with anorexia, malaise, headache, and backache, the temperature rising gradually to 39° centigrade. On admission, a coated tongue, relative bradycardia, splenomegaly, and a rose-colored rash were found. The number of leucocytes was 6,500, with 60 per cent neutrophiles, 31 per cent lymphocytes, and 6 per cent band-form neutrophiles. Widal agglutination test was positive. The fever continued for another fortnight, after which the patient gradually recovered. During the febrile period, two electrocardiograms were taken which were both normal (Fig. 2,*A*). During convalescence two electrocardiograms, taken at an interval of five days, showed identical changes: T_1 flat and T_2 and T_4 isoelectric (Fig. 2,*B*). On September 24, treatment with 500 mg. of niacin daily was started. After two days of treatment the T waves in Leads I, II, and IV showed a marked increase in voltage (Fig. 2,*C*). The electrocardiogram became normal and similar to that observed on admission.

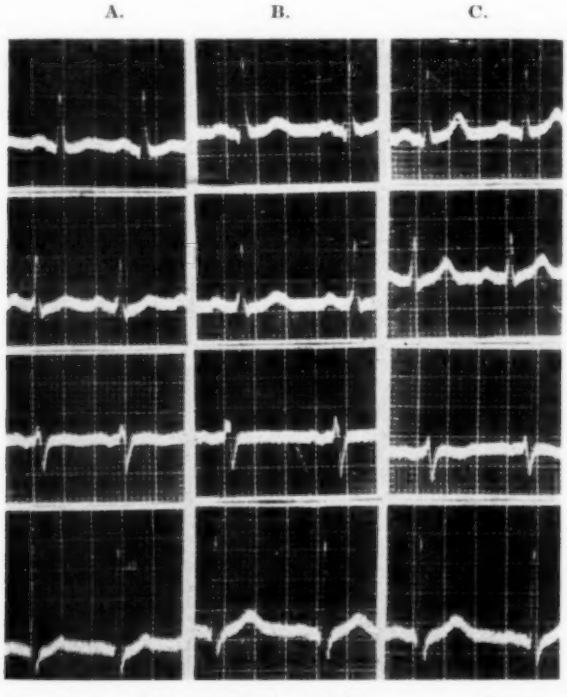

Fig. 3.—*A*, Electrocardiogram taken at the time of defervescence: flat T waves in all leads. *B*, After two days of niacin administration, increase in the voltage of T waves. *C*, Further elevation of the T waves after additional treatment of three days.

CASE 3.—R. L., a man, 45 years of age, was admitted on July 25, 1944, complaining of headache, anorexia, malaise, and fever which had started eight days prior to admission. During this period the temperature rose gradually to 39° centigrade. On admission, the patient was somnolent and showed bradycardia, splenomegaly, and a rose-colored rash on the abdomen. The number of leucocytes was 5,600, with 56 per cent neutrophiles, 40 per cent lymphocytes, and 4 per cent band-form neutrophiles. Eight days after admission, the Widal agglutination test was positive and typhoid bacilli were cultured from the bone marrow. The course of the disease was severe and sulfonamides were administered because of increasing toxemia. Intestinal bleeding occurred three weeks after admission, and two blood transfusions were given.

Five weeks after admission the temperature began to fall and gradually returned to normal within a fortnight. During defervescence, the patient complained of a burning sensation in the tongue; on examination the papillae were found to be atrophic and the color of the tongue was fiery red.

Two electrocardiograms were recorded during the febrile period, both of which were normal. At the time of defervescence, the T waves became flat in all leads (Fig. 3,*A*). Treatment with niacin, 500 mg. daily, was begun on September 5. After two days of niacin administration there was an increase in the voltage of the T wave in Leads I, II, and IV (Fig. 3,*B*). After three more days of treatment, further elevation of the T waves was observed (Fig. 3,*C*).

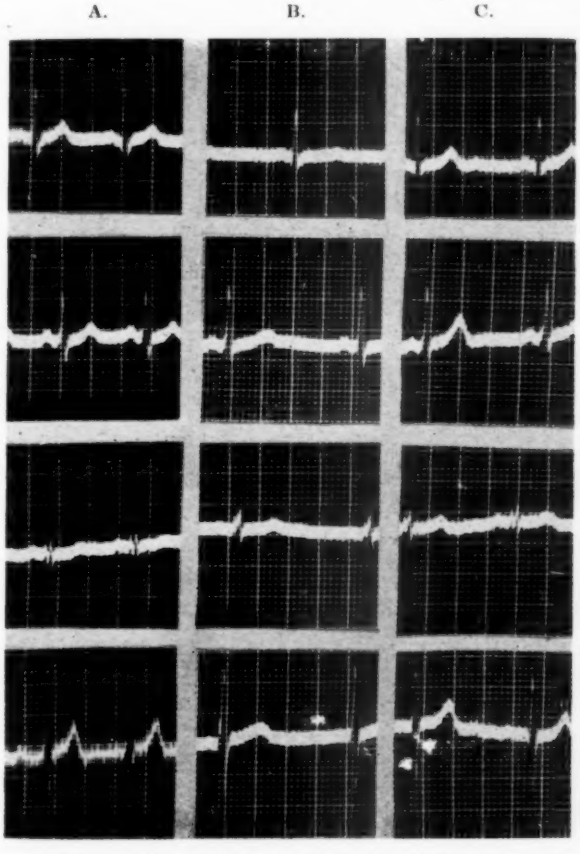

Fig. 4.—*A*, Normal electrocardiogram taken during the febrile period. *B*, Electrocardiogram taken during convalescence: T_1 almost isoelectric and T_2 and T_4 reduced. *C*, After three days' treatment with niacin, marked elevation of all T waves.

CASE 4.—N. B., a man, 23 years of age, was admitted on July 23, 1947, complaining of headache, malaise, and fever which had started three days earlier. On admission, the patient was in a state of somnolence; the main findings were bradycardia, splenomegaly and a coated tongue. The leucocyte count was 9,200, with 66 per cent neutrophiles, 17 per cent lymphocytes, 4 per cent monocytes and 13 per cent band-form neutrophiles. Widal agglutination test was positive. The fever rose gradually to 40° centigrade. The patient complained of severe headache, and five days after admission, there was a marked rigidity of the neck with positive Kernig sign. A lumbar puncture was performed but no pathologic findings were present in the cerebro-

spinal fluid. On the same day, treatment with penicillin, 200,000 units daily, was begun. The treatment was continued for one week, at the end of which period the temperature dropped to normal. The patient made an uneventful recovery.

A series of electrocardiograms was made during his stay in the hospital. On July 27, at the height of pyrexia, a normal electrocardiogram was obtained (Fig. 4,*A*). After the decline of the temperature, the T waves became flat and the electrocardiogram was definitely abnormal. In the period from August 2 to August 15, five records were taken, all of which showed similar alterations. Fig. 4,*B* shows the electrocardiogram taken on August 15: T_1 was almost isoelectric and T_2 and T_4 were flat. On the same day, treatment with niacin, 600 mg. daily, was started. After three days of this treatment a marked elevation of the T waves was noted and the record became normal (Fig. 4,*C*).

In twelve cases showing T-wave changes niacin was withheld, in order to follow the spontaneous regression of these alterations. In all but two of these cases a gradual improvement of the electrocardiographic pattern during the convalescent period could be observed. In this group, an average of twelve and one-half days was required for the restoration of the electrocardiogram to normal. In one patient, electrocardiographic abnormalities were still present twenty-six days after the fall of temperature, and follow-up was not possible. In the second patient, in whom the typhoid infection was severe and complicated by massive intestinal hemorrhages, the T waves became flat thirty days after the onset of the illness while the temperature was subfebrile. These changes were still present on his discharge eighteen days later and could not be further observed.

DISCUSSION

Our observations, as well as others reported in the literature, clearly demonstrate that electrocardiographic changes are of frequent occurrence in typhoid fever. Myocarditis due to the typhoid infection must be considered first among possible causes for these electrocardiographic findings. The assumption that myocarditis is responsible for the electrocardiographic changes in all cases appears improbable for the following reasons. There was a high frequency (70 per cent) of electrocardiographic abnormalities in our material, and it is unlikely that myocarditis was present in such a high percentage of cases. Pathologic studies in typhoid fever indicate that myocarditis is rare in this disease.[17] Slight to moderate toxic changes may be found in the heart muscle and interstitial tissue in patients dying of typhoid fever. The anatomic changes consist of cloudy swelling and infiltration with small round cells. Such findings are hardly to be expected in mild or moderate cases of typhoid fever.

The absence of clinical manifestations of cardiovascular involvement and the lack of parallelism between the severity of the disease and the presence and degree of electrocardiographic alterations cast further doubt on the assumption that myocarditis is the underlying cause of the cardiographic abnormalities. It appears, therefore, that the cause of the electrocardiographic alterations, should be sought rather in noninflammatory myocardial changes.

The change in the electrocardiographic pattern, which concerns mainly the final deflection of the ventricular complex, is frequently seen in metabolic disorders, such as alkalosis,[18] diabetic acidosis,[19] and vitamin B deficiency.[20] The

fact that the electrocardiographic alterations in our cases appeared during convalescence at a time when clinical manifestations of vitamin deficiency frequently appeared, as well as the absence of clinical signs of cardiac involvement, led to the assumption that the underlying cause of the electrocardiographic abnormalities was a metabolic disturbance in the heart muscle due to vitamin deficiency. The similarity of these changes to those seen in niacin deficiency justified the therapeutic trial of niacin. The effect of the administration of niacin was marked in all instances, and the electrocardiograms returned to normal after very short periods of treatment. In some cases striking improvement was observed after only two to three days of niacin administration. Thus, the response to niacin in patients with typhoid fever was similar to that in patients suffering from pellagra, and it is reasonable to suppose that the electrocardiographic changes in typhoid fever, as in pellagra, are due to niacin deficiency.

The rate of niacin excretion was examined during the course of the disease in nineteen cases. A uniform and gradual decrease of niacin excretion took place in all cases, the lowest excretion of niacin being found during convalescence. This decrease was explained by one of us (K.B.) as being due to increased requirements, disturbed intestinal synthesis and absorption, and the frequently low food intake during the course of the disease.[21] A definite relationship was observed between the level of niacin excretion and the electrocardiographic changes, the latter appearing at the time when the niacin excretion was at its lowest. The spontaneous improvement in the electrocardiogram in those cases which were not treated with niacin may be explained by the increased niacin content of the food during convalescence, the reduced requirements, and the improved absorption. This was indeed seen in four of these cases in which a spontaneous rise in the amount of niacin in the urine occurred late in convalescence.

It must, however, be borne in mind that deficiences may be multiple and that a lack of various components of the vitamin B complex may occur simultaneously. Peripheral neuritis, as seen in thiamine deficiency, was present in six of our cases. In fifteen cases the amount of pyruvic acid in the urine was also found to be markedly increased during the convalescent period. This finding also points to thiamine deficiency. Since the described electrocardiographic changes are not specific for niacin deficiency, they might also be caused by thiamine deficiency. The prompt therapeutic response to niacin treatment, however, supports the contention that the cause of the electrocardiographic changes is a deficiency of niacin.

SUMMARY

Serial electrocardiographic examinations were made in fifty cases of typhoid fever. In thirty-five cases, deviations from the normal were observed. The alterations were mainly present in the T waves, which became flat, isoelectric, or diphasic, usually after defervescence. Twenty-three patients with T-wave changes were given niacin which resulted in rapid normalization of the electrocardiogram. In twelve cases with pathologic electrocardiograms, a spontaneous gradual return to normal was observed.

The rapid effect of niacin and the development of the electrocardiographic changes concomitant with reduced niacin excretion in the urine is considered as evidence that the described electrocardiographic abnormalities are due to niacin deficiency.

REFERENCES

1. Thomson, K. J., Rutstein, D. P., Tolmach, D. M., and Walker, W. H.: Electrocardiographic Changes During and After Pneumococcus Pneumonia, AM. HEART J. **31**:565, 1946.
2. Dehn, H., Feil, H., and Rinderknecht, R. E.: Electrocardiographic Changes in Cases of Infectious Hepatitis, AM. HEART J. **31**:183, 1946.
3. Rosenberg, D. H.: Acute Myocarditis in Mumps, Arch. Int. Med. **76**:257, 1945.
4. Evans, W. F., and Graybiel, E.: Electrocardiographic Evidence of Cardiac Complications in Infectious Mononucleosis, Am. J. M. Sc. **211**:220, 1946.
5. Clerc, A., and Levy, J. R.: Récherches électrocardiographiques au cours de fièvre typhoide, Compt. rend. Soc. de biol. **100**:1072, 1929.
6. Arieff, M. J., and Tigi, R. R.: Elektrokardiographische Beobachtungen bei Typhus abdominalis, Ztschr. f. klin. Med. **112**:641, 1930.
7. Chagas, E.: Contribution a L'Etude des Alterations du coeur dans la fièvre typhoid, Compt. rend. Soc. de biol. **106**:505, 1931.
8. Bucham, E. S. P., and Daniels, L. P.: Electrocardiographische Untersuchungen bei akuten Infektionskrankheiten, Deutsches Arch. f. klin. Med. **174**:250, 1932.
9. Lukomski, P.: Elektrocardiographische Beobachtungen bei Abdominaltyphus und Pneumonie, Deutsches Arch. f. klin, Med. **174**:586, 1932.
10. Gurewitsch, F. D.: Besonderheiten des Herzgefaesssystems der Kinder in der Rekonvaleszenz nach Typhus abdominalis, Monatschr. f. Kinderh. **64**:341, 1936.
11. Giraud-Costa, Pr., and Raybaud, M. L.: Rev. med. franc. du Moyen Orient **2**:1, 1943.
12. Brow, G. B.: The Heart in Typhoid Fever, Canad. M. A. J. **20**:606, 1929.
13. Porter, W. B., and Bloom, N.: The Heart in Typhoid Fever, AM. HEART J. **10**:793, 1935.
14. Stuart, B. M., and Pullen, R. L.: Typhoid, Clinical Analysis of 360 Cases, Arch. Int. Med. **78**:629, 1946.
15. Cheer, S. N., and Dieuaide, F. R.: Studies on Electrical Systole (Q-T Interval) of Heart; Its Duration in Cardiac Failure, J. Clin. Investigation **10**:889, 1931.
16. (a) Rachmilewitz, M., and Braun, K.: Presence of Electrocardiographic Changes in Nicotinic Acid Deficiency and Their Elimination by Nicotinic Acid, AM. HEART J. **27**:203, 1944.
    (b) Rachmilewitz, M., and Braun, K.: Electrocardiographic Changes and the Effect of Niacin Therapy in Pellagra, Brit. Heart J. **7**:72, 1945.
17. Kaufmann, R.: Spezielle Pathologische Anatomie, Berlin, 1931, W. de Gruyter & Co., Vol. 1, p. 53.
18. Basher, P. S., Shrader, E. L., and Ronzoni, E.: The Effects of Alkalosis and of Acidosis Upon the Human Electrocardiogram, AM. HEART J. **17**:169, 1939.
19. Bellet, S., and Dyer, W. W.: The Electrocardiogram During and After Emergence From Diabetic Coma, AM. HEART J. **13**:72, 1937.
20. Weiss, S., and Wilkins, R. W.: The Nature of the Cardiovascular Distrubances in Nutritional Deficiencies (Beriberi), Ann. Int. Med. **11**:104, 1937.
21. Braun, K., and Grossowitz, N.: Niacin Excretion in Typhoid Fever, Arch. Int. Med. **80**:637, 1947.

Clinical Reports

BILATERAL NONTRAUMATIC ILIOFEMORAL THROMBOPHLEBITIS IN A CHILD

H. L. Myers, M.D., and N. Artsis, M.D.
Oceanside, N. Y.

ILIOFEMORAL thrombophlebitis, though commonly seen in adults, is rare in children. In a series of 254 cases of thrombophlebitis of the iliofemoral vein reported by Allen, Barker, and Hines,[1,2] the youngest patient was 10 years of age. The following case is an example of nontraumatic iliofemoral thrombophlebitis in a 6-year-old child. The onset followed an ill-defined respiratory and gastrointestinal infection.

N. D., a 6-year-old school boy with essentially normal family, past, and birth histories, had a mild upper respiratory infection early in May, 1947. This was characterized by a moderate fever, swelling of the glands of the left cervical region, general malaise, and followed by a brief attack of diarrhea. During the acute episode a diagnosis of "mumps" was made by the family physician. The correctness of this diagnosis was in doubt. The patient apparently recovered from this acute illness after a period of about ten days and returned to school. Several days later he had some pain in the region of the left buttock, associated with slight fever and inability to walk or sit down on that side. Within forty-eight hours pain and fever had subsided and the patient was up and about for two days. On the third day the child developed fever, diarrhea, and abdominal pain. At that time a diagnosis of "intestinal grippe" was made. After a few days of bed rest the diarrhea subsided and then the patient began to develop pain in the left thigh and leg. Examination on May 18, 1947, revealed an acutely ill child with a swollen left lower extremity. The swelling extended from the inguinal ligament to the tips of the toes. The left iliac pulse was barely palpable. It was the most distal palpable pulse in the left lower extremity. The left great toe was 4° F. (2.2° C.) cooler than the right by skin thermocouple test. The right iliac pulse was easily palpated. The right popliteal pulse could be palpated but the anterior and posterior tibial pulses on the right side were not palpable.

On May 19, 1947, the left iliac pulse could not be felt. The left foot assumed a slate blue cyanosis and was 10° F. (5.5° C.) cooler than the right when tested with a skin thermocouple on the plantar aspect of the great toes. A left paravertebral block was performed at the levels of the second, third, and fourth lumbar sympathetic ganglia. Patient was initially anesthetized by open drop ether; 3.0 c.c. of 1 per cent procaine was placed into each space and this was followed by 2.5 c.c. of Bromsalizol in oil.[3]

On May 20, 1947, there was marked improvement in the appearance of the left lower extremity; the left foot was only slightly cooler than the right and there was a marked reduction in the tension of the tissues. The temperature had dropped to 100° F. (37.7° C.) and pain was

From the South Nassau Communities Hospital, Oceanside, New York.
Received for publication July 21, 1947.

completely relieved. The penicillin therapy which had been started on May 18, 1947, 30,000 units every three hours, was continued.

During the next few days the general and local condition continued to improve; but on May 22, 1947, the patient began to develop pain and swelling in the right lower extremity. The right iliofemoral pulse was not palpable and the right leg began to become cold, cyanotic, and painful. A paravertebral block was performed on the right side, using the same technique that was used on the left. An immediate improvement in pain, swelling, and tenderness was noted. By May 31, 1947, the general condition had improved sufficiently for the patient to be up and around with bilateral elastic bandages from instep to the tibial tubercle.

During the interim immediately following the second block, the patient refused to extend his lower extremities and held them flexed toward the abdomen. Edema developed in both feet and, in order to avoid contracture and stasis, Buck's extensions were set up with 3-pound weights for each leg. This was well tolerated by the patient and succeeded in overcoming the persistent flexion at the knee and hip. Patient also developed a mild secondary anemia for which two transfusions, each of 250 c.c. citrated blood, were given.

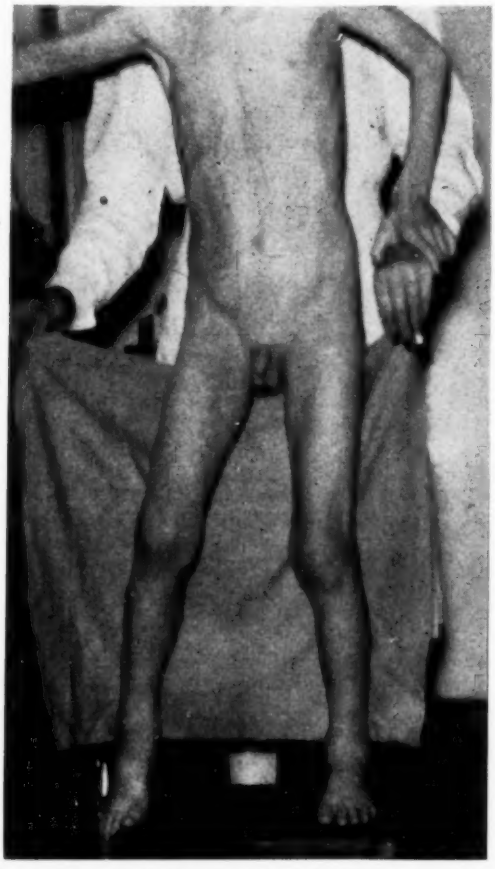

Fig. 1.—Note prominent veins on abdomen. This photograph was taken twenty days after the onset of acute swelling in the left (initial) lower extremity. Patient was up and around with elastic bandages from instep to knee.

Laboratory Work.—On May 18, 1947, the urine was negative except for a faint trace of acetone. The blood count on May 19, 1947, showed a hemoglobin of 11.6 grams (80%) with 4.2 million red cells. The white cell count was 22,500, with 92 segmented forms, 6 lymphocytes, 1 monocyte

and 1 basophile. On May 23, 1947, there was a reduction in the red cell count to 3.5 million and in the hemoglobin to 9.09 grams. The white blood cells remained about the same, both in number and differential count. By May 28, 1947, the hemoglobin had improved somewhat, having increased to 9.9 grams with no increase in the erythrocyte count. The leucocytes remained unchanged. The count on June 5, 1947, revealed a hemoglobin of 11.3 grams, with 3.2 million erythrocytes and 10,300 white blood cells, with 74 segmented forms, 25 lymphocytes, and 1 eosinophile. Tests for the Rh factor were positive, blood group 0, and the Wassermann reaction was negative. On June 6, 1947, heterophile antibody was found to be 1 plus in a 1:16 dilution. An x-ray film of the pelvis disclosed no abnormal findings in the bones or joints.

On discharge the patient had prominent abdominal collateral veins which were still present three months later. He developed dependent edema if legs were unsupported by his elastic stockings. Four weeks after discharge from the hospital the abdominal collateral veins were still prominent, especially on standing upright. There was slight edema on prolonged dependency when the elastic stockings were not worn. All the major peripheral pulses were palpable in both lower extremities. There was dependent cyanosis of the feet but no marked skin discoloration, perspiration, or other vasomotor phenomena seen in late stages of thrombophlebitis (Fig. 1).

The diagnosis was bilateral iliofemoral thrombophlebitis. The etiology was unknown but the onset may have been associated with the acute condition which has been described.

DISCUSSION

According to Ehrich and Krumbaar,[4] predisposition to iliofemoral thrombophlebitis is more likely based on a developmental rather than a congenital abnormality. Compression exerted upon the left common iliac vein by the right common iliac artery contributes to the production of developmental defects which predispose to deformity of the vein lumen. This probably accounts for the greater frequency of left- over right-sided iliofemoral thrombophlebitis. Extension of this process from the left into the right common iliac to produce the "horseshoe thrombophlebitis" is the usual course of events. Disappearance of the arterial pulsations in first the left and then the right lower extremity follows the spread of the thrombophlebitic process. It is interesting to note the absence of the distal pulses in the right lower extremity at the time when the process was confined to the left.

Therapy consisted of elevation of the foot of the bed on eight-inch blocks, warm fomentations, penicillin, 30,000 units every three hours, and paravertebral sympathetic nerve blocks. Bromsalizol was used in order to prolong the effect of the blocks and obviate the necessity for repeated blocking. The administration of a general anesthesia was necessary in order to carry out these blocks in a child.

The question of the use of anticoagulants was debated. Finally it was decided that this therapy should not be used for the following reasons: It would be extremely difficult to administer intravenous therapy in view of the scarcity of accessible veins. The daily prothrombin determinations required to adequately control Dicumarol in a child would be extremely difficult to obtain in view of the inaccessibility of venous blood. Such therapy, although well-standardized as to dosage in adults, has apparently not been very widely used in pediatric practice. If any anticoagulant had been selected, heparin rather than Dicumarol would have been the drug of choice. Possibly the new intramuscular preparation of heparin in Pitkin's menstruum, described by Loewe and Hirsch,[5] might have

offered a means of administering heparin in this case. The use of heparin in Pitkin's menstruum was considered but discarded because the arms were so small and thin that there was no place into which to inject the heparin. The lower extremities were involved in the thrombophlebitic process. Introduction of heparin into these members might aggravate the existing thrombophlebitis. The transfusions were administered as a means of supportive therapy and in order to overcome the thrombophilic tendency which exists in the presence of anemia.

This patient has had elastic stockings made to his measure and will continue to wear them until dependent edema no longer develops. He may subsequently develop superficial varicosities in his lower extremities which can be handled in the usual manner after the deep circulation has been re-established.

SUMMARY

A case of bilateral nontraumatic iliofemoral thrombophlebitis in a 6-year-old child is presented. The etiology, management, and prognosis of this case are discussed.

ADDENDUM

The following observations were made on a follow-up visit May 15, 1948. General health was very good. There were no complaints. The edema of the lower extemities had subsided completely. Supporting bandages were no longer required. The superficial veins of both lower extremities were normal. There were no obvious varicose veins. The abdominal collateral veins were still quite prominent.

REFERENCES

1. Allen, E. V., Barker, W. W., and Hines, E. A.: Peripheral Vascular Diseases, Philadelphia, 1946, W. B. Saunders Company, pp. 617-622.
2. Barker, W. W.: Thrombophlebitis Complicating Infections and Systemic Diseases, Proc. Staff Meet., Mayo Clin. **11**:513, 1936.
3. Lee, F. C., Macht, D. I., and Pierpont, R. Z.: The Use of Bromsalizol in Lengthening the Effect of a Sympathetic Nerve Block, Am. J. M. Sc. **209**:314, 1945.
4. Ehrich, W. E., and Krumbaar, E. B.: A Frequent Obstructive Anomaly of the Mouth of the Left Common Iliac Vein, AM. HEART J. **26**:737, 1943.
5. Loewe, L., and Hirsch, E.: Heparin and Thromboembolic Disease, J. A. M. A. **133**:1263, 1947.

HEMIPLEGIA FOLLOWING CAROTID SINUS STIMULATION

A Case Report

E. S. Brannon, M.D.
Rome, Ga.

A CASE report of hemiplegia following trauma to the contralateral carotid sinus is brought to the attention of the reader, as there are only a few authentic cases of this nature.

CASE REPORT

A 60-year-old carpenter was on his knees boring a hole in a floor with a brace and bit when, as the bit suddenly went through the floor, he struck the right side of his neck against the end of an upright pipe. The site of injury was just beneath the angle of the right mandible. Approximately three minutes after this accident the left upper extremity exhibited clonic convulsive movements for a very short while. He did not lose consciousness and was able to continue work with his right hand. Approximately ten minutes after the accident, his wife found him in an adjacent room and observed that he was not able to use either the left upper or the left lower extremity. He was also somewhat confused. Further history obtained from his wife and brother revealed no evidence of pre-existing disease, hypertension, or declining health.

Physical examination revealed a man who was confused and kept his head turned to the right side. The muscles of the left side of the face were flaccid. The pupils and ocular fundi showed no abnormalities. The neck was not stiff and there was no swelling or discoloration at the site of injury. The blood pressure was 144/90. The heart rate was 48 per minute and the rhythm was regular. No heart murmur was heard. The radial pulses were equal and synchronous. The liver and spleen were not felt. On the left side the deep reflexes were absent and the muscles were flaccid. Urinalysis was normal, the red blood cell count and hemoglobin showed a slight degree of anemia, and the white blood cell count was slightly elevated with a normal differential. Spinal fluid pressure was not increased, the cell count was 5, protein was not increased, and the Kahn test was negative. A serologic test for syphilis (Kahn) was likewise negative. Electrocardiogram revealed no abnormalities.

The patient's temperature remained normal throughout his two weeks' stay in the hospital. He showed slight improvement in his ability to use the left lower extremity during the latter part of his stay in the hospital. When seen one year after the accident, his general state of nutrition was good. He recognized the author as the one who attended him while in the hospital although he was still not mentally alert after one year. The chief neurologic signs of significance at that time were confined to the left upper and left lower extremity. These consisted of spasticity of the muscles, hyperactive reflexes, grasp reflex, ankle clonus, and Babinski's sign.

DISCUSSION

Although aware of the numerous causes of hemiplegia in a 60-year-old man, one was immediately impressed by the sequence of events which followed injury

Received for publication June 19, 1947.

in this case. The site of the impact was in the region of the right carotid sinus. Within three minutes following the blow, clonic convulsive movements developed in the contralateral upper extremity. Within ten minutes after injury, hemiplegia of the contralateral side was present.

The fact that the patient received a blow rather than manipulation of the carotid sinus should not distract from the assumption that carotid sinus stimulation was the cause of the subsequent events. It is postulated that the impact to the region of his right carotid sinus reflexly produced cerebral arterial constriction, manifested by the clonic convulsions of the left upper extremity. The arterial constriction was most likely followed by occlusion of a branch of the right anterior cerebral artery. Cerebral arteriosclerotic changes may well have contributed to this accident. The cases reported by Marmor and Sapirstein[1] showed peripheral and retinal arteriosclerosis as well as cerebral arteriosclerosis. Three of the cases reported by Askey[2] had arteriosclerosis. What role the hemodynamics, other than the local alterations caused by cerebral arterial constriction, contributed to the formation of a cerebral vascular thrombus is difficult to say. Although temporary asystole, bradycardia, or a decline in blood pressure may occur following carotid sinus stimulation, and thus may enhance the formation of a cerebral arterial thrombus, local cerebral phenomena may appear following carotid sinus stimulation without evidence of systemic circulatory changes.[2,3]

SUMMARY

1. A case report is given of a patient who developed hemiplegia shortly after receiving trauma to the contralateral carotid sinus.

2. It is postulated that his first symptoms resulted from cortical ischemia due to localized cerebral arterial constriction of reflex origin; furthermore, that thrombosis of the right anterior cerebral artery occurred and resulted in hemiplegia which was still present one year after the accident.

REFERENCES

1. Marmor, Judah, and Sapirstein, M. R.: Bilateral Thrombosis of Anterior Cerebral Artery Following Stimulation of a Hyperactive Carotid Sinus, J. A. M. A. **117**:1089, 1941.
2. Askey, J. M.: Hemiplegia Following Carotid Sinus Stimulation, Am. Heart J. **31**:131, 1946.
3. Engel, G. L., Romano, J., and McLin, T. R.: Vasopressor and Carotid Sinus Syncope. Clinical, Electroencephalographic and Electrocardiographic Observations, Arch. Int. Med. **74**:100, 1944.

Abstracts and Reviews

Selected Abstracts

Hand, A.: Cerebral Abscess; A Complication of Congenital Cardiac Disease (Fallot's Tetralogy). J. Pediat. **31**:662 (Dec.), 1947.

A 4½-year-old cyanotic boy developed an upper respiratory infection, temperature, bradycardia, headache, vomiting, and convulsions. Brain abscess was suspected and trephination in the left temporal region permitted the evacuation of 42 c.c. of yellowish-green turbid fluid. The child died two days later.

Pulmonary stenosis, interventricular septal defect, and hypertrophy of both ventricles were found at necropsy. There was no mention of dextroposition of the aorta. Three separate brain abscesses were found: one in the left temporosphenoidal region, another in the left occipital lobe, and the third in the left parietal area. Attention is drawn to the frequency of brain abscess as a complication of congenital heart disease.

HAUB.

Shumacker H. B., Jr., Abramson, D. I., and Lampert, H. H.: The Use of Anticoagulants in the Surgery of Aneurysms and Arteriovenous Fistulas, With Particular Reference to Dicumarol. Surgery **22**:910 (Dec.), 1947.

The authors presented their experiences with the use of anticoagulants in the prevention of thrombosis following various types of repair of peripheral arterial and arteriovenous fistulas. In a number of cases, dicumarol was given before operation, with the result that at the time of surgery an adequate reduction in prothrombin level had already been attained. Despite this, no particular difficulty with hemostasis was experienced in the operative field. As a safeguard, fibrin foam was often placed in the wound. In several cases, however, some later complications occurred, such as hematoma formation. Nevertheless, the authors expressed the opinion that reparative procedures upon peripheral arteries can safely be undertaken when a full anticoagulant effect has already been achieved with heparin, dicumarol, or both. Furthermore, they believed that they had obtained at least suggestive evidence for the view that such therapy renders less likely thrombosis of the repaired segment of artery.

ABRAMSON.

Watson, W. L.: Pulmonary Arteriovenous Aneurysm. A New Surgical Disease. Surgery **22**:919 (Dec.), 1947.

The author described a rare condition, nontraumatic pulmonary arteriovenous aneurysm, consisting of a lobulated, thin-walled, branching, pulsating pulmonary sac of varying size, made up of both an arterial and a venous component. This structure produces a shunt in the lung whereby a considerable amount of blood passes from the arterial to the venous portions of the pulmonary circuit without passing through the alveolae of the lung to be oxygenated. This results in a low oxygen saturation of the arterial blood in the systemic circulation and the various changes consequent to such a condition.

On the basis of ten previous reports of such cases and two of his own, the author presented the pertinent points upon which a diagnosis of pulmonary arteriovenous aneurysm can be made.

All but two cases were men, most of the reported ages falling between 17 and 30 years. Persistent cyanosis of the face, hands, and feet, clubbing of the fingers and toes, and high red blood count and hemoglobin were common findings. Half of the patients complained of exertional dyspnea, but the heart, electrocardiogram, and blood pressure were not abnormal. X-ray films in each instance showed a branching, lobulated mass of uniform density in the lung field. Other diagnostic features were hemoptysis, epileptiform seizures, a normal spleen, and normal sternal puncture studies.

Polycythemia vera was ruled out by the age of the patient, the lack of splenomegaly, and a normal range of white blood cell and platelet counts. The absence of a history of exposure to high altitude or poisoning by heavy metals or aniline dyes eliminated the possibility of secondary polycythemia. Similarly, cardiac anomalies with a right to left shunt or chronic pulmonary disease preventing adequate oxygenation were ruled out by roentgenographic and electrocardiographic findings.

In the treatment of the condition, repeated venesections, phenylhydrazine, and surgical intervention have been employed. In the author's two cases, ligation of the artery feeding the aneurysm was carried out in one case, and in the other, the involved portion of the lung as well as the aneurysm were excised. The results in both cases were quite satisfactory; the high hematocrit, red blood cell volume, and the arterial oxygen saturation returned to normal.

ABRAMSON.

Blackford, L. M.: Calcification of the Myocardium. Ann. Int. Med. 27:1036 (Dec.), 1947.

Nine years before death, a 59-year-old white man had suffered an acute myocardial infarction due to thrombosis of the left anterior descending branch of the left coronary artery. He remained relatively asymptomatic following this episode. Death was due to the rapid development of left ventricular failure and a terminal thrombotic occlusion of the right coronary artery. At necropsy, the significant findings consisted of the following: The anterior surface of the left ventricle and the apex felt like bone. The pericardium was plastered against this part of the heart and there were also adhesions between the heart and the diaphragmatic surface of the pericardium. The anterior descending branch of the left coronary artery had been obliterated about 2 cm. below the bifurcation. Distal to this point, the heart was ballooned out to form a ventricular aneurysm and the myocardium was largely replaced by calcific bonelike material. The infarcted area was roughly circular, 8 cm. in diameter; its inner surface was rough.

WENDKOS.

Glaser, R. J., Dankner, A., Mathes, S. B., and Harford, C. G.: Effect of Penicillin on the Bacteremia Following Dental Extraction. Am. J. Med. 4:55 (Jan.), 1948.

Since the bacteremia which often follows dental extraction is believed to be of importance in the pathogenisis of subacute bacterial endocarditis, the authors have attempted to evaluate the efficiency of penicillin as a prophylactic agent in preventing such bacteremia. The results in a control series of forty patients are compared with those in a group of forty patients who received 600,000 units of penicillin in divided doses during the twenty-four hours preceding extraction. It is apparent from the results that penicillin, while effective in reducing the incidence of bacteremia after tooth extraction, did not prevent its occurrence in a large number of patients. It is suggested from the data that it may be desirable to extract teeth singly when penicillin prophylaxis is indicated.

WOODS.

Mufson, I., Quimby, E. H., and Smith, B. C.: Use of Radioactive Sodium as a Guide to the Efficiency of Drugs Used in Treatment of Diseases of the Peripheral Vascular System. Am. J. Med. 4:73 (Jan.), 1948.

Utilizing the radioactive isotopes of sodium according to the method of Smith and Quimby, the authors have studied the effects of drugs used in the treatment of peripheral vascular disease.

The radioactive material was introduced into the circulation by intravenous injection and its accumulation in the extravascular fluid in an extremity noted with a Geiger counter. This accumulation is dependent upon the patency of the minute vessels, the vascularity of the area, and the permeability of the capillary endothelium. An acceleration in rate should therefore be indicative of dilatation of the minute vessels and an increase in available semipermeable membrane.

Of the drugs tested, only histamine appeared able to produce an immediate increase in capillary diffusion rate as determined by a radiosodium curve taken following a single dose. Intra-arterial injection or iontophoresis are said to be the most efficient routes for the introduction of histamine in these tests. Neither papaverine nor 5 per cent sodium chloride given intravenously produced changes in the radioactive sodium curves.

WOODS.

Wagner, B. M.: Penicillin Therapy in Subacute Bacterial Endocarditis. Am. J. M. Sc. **215**:84 (Jan.), 1948.

This article contains an analysis of reports in the literature of the treatment of 521 cases of subacute bacterial endocarditis with penicillin. Clinical arrest was effected in 371 patients (71.3 per cent) who have continued to remain well. In an additional ninety-five patients (18.2 per cent), a "cure" was produced in the hospital, but the disease recurred and the patients died within three to four months. No autopsies were performed in this group. The remaining fifty-five cases (10.5 per cent) were complete clinical failures.

The following principles of treatment were considered to be amply justified by this composite experience: 1. The sensitivity of the infecting organism to penicillin should be determined in vitro within a range of 0.1 to 1 unit per cubic centimeter. 2. If the organism is sensitive, the dosage of penicillin should be 500,000 units daily by continuous intravenous drip. 3. All cases should be treated as early as possible. 4. Therapy should be continued for at least twenty-eight days. If the patient's condition does not improve, 1,000,000 units should be given daily for twenty-eight more days. 5. The plasma level of penicillin and the sensitivity of the organism to penicillin in vitro should be determined twice a week.

DURANT.

Plotz, M.: Progress of Medical Science: Non-Atheromatous Lesions of the Coronary Arteries. Am. J. M. Sc. **215**:91 (Jan.), 1948.

The most important disease of the coronary arteries is atheromatosis. Ninety to 95 per cent of all cases of myocardial infarction result from changes in and around an atheromatous plaque which result in reduction of the blood supply to the affected area. Other lesions of the coronary arteries are clinical curiosities and scant attention has been given to them. It is the purpose of this report to classify these changes and gather in one place the knowledge, especially in the way of recent advances, now scattered throughout the literature. Only the salient features are discussed, but most of the important late and key references are given for further study.

The following classification of non-atheromatous lesions is used as a basis for the review:

1. Congenital anomalies, including especially:
   Single coronary artery
   Origin from pulmonary artery (left coronary, right coronary, or both)
   Origin of an accessory coronary artery from the pulmonary artery
   Hypoplasia
2. Medial calcification with fibroblastic proliferation of the intima
3. Inflammatory lesions:
   A. Specific infectious diseases
      Syphilis
      Tuberculosis
      Other bacterial infections

B. Arteritis of unknown etiology
Rheumatic fever
Periarteritis nodosa
Thromboangiitis obliterans

4. Aneurysms
5. Embolic and thrombotic disease
6. Neoplasm

DURANT.

Saphir, Otto, and Leroy, Elie P.: True Aneurisms of the Mitral Valve in Subacute Bacterial Endocarditis. Am. J. Path. 24:83 (Jan.), 1948.

In subacute bacterial endocarditis, mycotic aneurysms of the aortic and mitral valves are not rare. These are the result of erosion of a leaflet with cup-shaped deformity filled in with a layer of thrombotic material. A roughened necrotic valvular surface may eventually be covered with granular repair tissue, but in the course of this destructive and repair process, the valve may outpouch as a result of the force of blood current, and thus show a saccular deformity. Controversy exists as to the terms "false" versus "true" valvular aneurysm.

The writers noted twelve instances of valvular aneurysm in thirteen patients with subacute bacterial endocarditis. All were on the mitral valve. Five of these aneurysms were deemed to be "true" aneurysms, four of them on the anterior mitral leaflet and one on the posterior. They all were well circumscribed, with round, smooth outpouching of a part of the involved mitral leaflet. Gentle compression accentuated the aneurysmal outpouching, at the apex of which there was a small perforation in four instances. In one case, there were multiple small aneurysms. In all instances, the ventricular surface of the anterior (aortic) mitral leaflet was thickened and fibrotic. Small, round defects with thickened margins were the sites of the aneurysms, all of which bulged in the direction of the left atrium. These defects were really entrances, the aneurysm-depressions having a larger diameter. Thrombi and blood filled the depressions.

Microscopy revealed local thinning and loss of elastic lamellae of the zona ventricularis and reduction of the deeper zona fibrosa. Inflammatory cells infiltrated the area, and at the most involved point only the endothelial layer of the opposite side of the valve was intact.

The definition of a "true" aneurysm involves more than mere ulceration; granulation processes and scar formation with subsequent saclike outpouching constitute the lesion.

The writers point out an interesting clinical correlation. These patients with valvular aneurysm received large doses of penicillin, sometimes in association with sulfonamides. The clinical course was accordingly more protracted. In this connection a review of the clinical data of Libman and Friedberg is of interest. Working in the prepenicillin era, they described aneurysmal defects of the mitral valve in subacute bacterial endocarditis in the protracted bacteria-free stages of the disease. Some spontaneous tendency to healing of lesions is definitely implied in that observation.

The modern treatment that has shown such striking curative effects will in some instances be nullified by the accompanying developments of fibrotic valvulitis, aneursym, and valve rupture.

GOULEY.

Fawcett, R. M.: Myocardium After Sulfonamide Therapy. Arch. Path. 45:25 (Jan.), 1948.

This study was stimulated by recent reports in the literature indicating that sulfonamide therapy was the cause of interstitial myocarditis, which, at least from the standpoint of microscopy, was far more extensive than generally realized. Fawcett emphasizes that whereas sulfa drugs have been widely used, and sensitivity to such therapy has been definitely established in some patients, the clinical incidence of interstitial myocarditis is no greater than in the pre-sulfonamide era.

Using as a criterion that type of cardiac involvement known in the literature as Fiedler's myocarditis or idiopathic myocarditis, the author points out that at the Mayo Clinic there has

been no increase in such myocardial involvements in comparing two five-year periods, one before and one after the common use of sulfonamides. Gross examination of hearts in the first period previous to 1935 and of hearts in the later period from patients who had received sulfonamide therapy, revealed no changes that might be attributed to therapy. Microscopic examination of hearts from the two periods showed no significant or constant differences between the control group and those patients who had received sulfonamide drugs in large amounts. Within each group there was a great variation of myocardial fiber damage and cellular infiltrations.

The author then examined 100 cases in which there had been sulfonamide therapy, including thirty subjected to massive dosage. There were in addition two patients who were found sensitive to the drug and who were known to have an interstitial myocarditis. This large group was matched with an equally large control group in which many patients died of infection but who had not been similarly treated. All cases with myocardial involvement due to rheumatic fever, diphtheria, syphilis, and myocardial infarction, and those with more than moderate coronary artery sclerosis were excluded. The numbers and types of the infiltrating cells in the heart sections were recorded in every case. Since the sections were of varying size, the quantitive estimate could not be accurate, but this handicap was common in both groups.

A comparative study of the sulfonamide-treated group and the control group showed no significant difference in the grading of cell types or of the increase of such cells infiltrating the myocardium. No significant difference could be found in the number of cells of any type, either in the auricular or the ventricular myocardium. This included eosinophilic infiltration, which has been stressed by previous writers.

In thirteen of twenty cases of the sulfonamide group in which the history suggested drug sensitivity, there was no increase in cellular infiltration; in only one of the twenty was there a plus 3 cellular infiltration.

All of the sulfa drugs currently used from 1935 to 1940, from sulfanilamide to sulfadiazine, were represented in this report which sharply negates clinical impressions and previous studies, dealing with "sulfonamide myocarditis."

GOULEY.

Maynard, R. M., and Thompson, C. W.: Congenital Aneurysm of an Aortic Sinus. Arch. Path. 45:65 (Jan.), 1948.

The writers report a case of congenital aneurysm of the sinuses of Valsalva occurring in a 23-year-old white man who suddenly developed substernal pain which radiated down both arms and was accompanied by a state of shock. On the day following this attack, there were moderate fever, reddish colored urine, and continuous substernal pain accompanied by soreness in the upper part of the abdomen. The slightest exertion brought on dyspnea.

The blood pressure was 156/20 in both arms; a Corrigan pulse and a pistol shot femoral sound were noted. There was a systolic thrill to the left of the sternum, and to-and-fro murmurs were heard over the precordium, loudest in the tricuspid area. The spleen was not palpable. At no time was there a positive blood culture. The past medical history was irrelevant.

In view of the fever and leucocytosis, penicillin therapy was instituted. One week after the onset of this attack, it was clear that the patient was suffering from congestive heart failure which was verified by marked prolongation of circulation time, by high venous pressure, and by x-ray study. The patient's condition gradually grew worse and death occurred eighteen days after the acute onset.

Necropsy revealed a right hydrothorax, but only a small amount of pulmonary edema. The heart was of slightly increased weight and showed a patency connecting a deficiency in the posterior sinus of Valsalva with a sacular outpouching into the right atrium. This sacculation was situated at the annulus fibrosus in the area of the medial leaflet of the tricuspid valve. The sac opened widely into the atrium. The other valves were normal. The foramen ovale was closed. The interventricular septum was intact. The pulmonary aorta was normal. The liver showed a nutmeg mottling throughout.

Microscopic examination revealed no inflammatory reaction in the wall of the aneurysm nor of the patency extending into the right auricle. The aortic wall showed nothing of note. The

lungs showed edematous interstitial tissue and in some areas large numbers of neutrophils. The spleen was normal.

It is believed that the severe chest pain and shock were caused by rupture of a congenital aneurysm. The electrocardiographic examination did not yield data of diagnostic importance.

GOULEY.

Larkin, M. A.: Abdominal Symptoms in Sudden Acute Heart Conditions. Am. J. Surg. 74:49 (July), 1947.

The author begins with a discussion of the visceral afferent innervation of the heart and the abdominal organs. The visceral afferent impulses course through the thoracolumbar sympathetic chain and, therefore, "it is evident that pain sensation from two unrelated systems, the heart and upper abdominal contents, can bombard the spinal cord in two complete and identical segments."

Larkin then discusses ninety-two cases with acute cardiac conditions, all but one being the result of coronary occlusions. The mortality for the entire group was 53.3 per cent. Twenty patients had abdominal symptoms which included pain, nausea, and vomiting. Seven of the twenty experienced abdominal pain only and six had only nausea and vomiting. Seven patients of the group suffered from abdominal pain and nausea and vomiting. Larkin cites a case history in which an exploratory laparotomy was performed for a suspected perforated ulcer in a 34-year-old white man. Death occurred on the second post-operative day and autopsy showed a rupture of the posterior wall of the left ventricle secondary to thrombosis of the right coronary artery and also a benign duodenal ulcer.

The author closes by discussing the differential diagnostic aids which may distinguish between an acute condition of the heart and one in the abdomen. These include the blood count, electrocardiogram, and the flat x-ray plate of the abdomen.

LORD.

Lindroth, L. V.: Sympathetic Nerve Block in Hypertension and Allied Cases. Am. J. Surg. 74:66 (July), 1947.

The author describes his technique of injecting absolute alcohol paravertebrally from the ninth through the twelfth thoracic sympathectic ganglia in two stages in the treatment of hypertension. General anesthesia is employed. Four cases are tabulated and the history of one patient is outlined. The advantages of the procedure over surgical thoracolumbar sympathectomy are the ease of performance, the slighter trauma to the patient, and the opportunity it affords to treat seriously ill patients who could not survive surgical intervention.

LORD.

Langley, G. J., and Platt, R.: Hypertension and Unilateral Kidney Disease. Quart. J. Med. 16:143 (July), 1947.

The purpose of this paper is to formulate the indications for nephrectomy in hypertension. The authors collected ninety-three cases from literature and added ten previously unpublished cases.

In forty-seven cases, the blood pressure was restored to normal and remained normal for the period in which the cases were followed, usually more than a year. In thirty-seven cases, no significant reduction of the blood pressure followed the operation; in some cases, it was higher after the operation. In six cases, there was a significant fall in pressure, though not to normal. In thirteen cases, the result was doubtful because of inadequate data or short follow-up period.

Age, of itself, did not contraindicate operation. Of sixteen patients over 45 years of age, eleven were cured and five were unimproved by nephrectomy. In forty-eight cases in which the retinal changes were studied, these changes appeared to have little prognostic significance. Of thirteen cases with a family history of hypertension, operation was successful in only one, whereas in thirteen cases in which the family history was stated to be negative, operation was successful in eight.

Of twenty-seven cases of pyelonephritis, seventeen had a successful result. Pyelonephritis was the lesion found in five cases with a positive family history of hypertension and in six with a negative family history. There were sixteen cases in which calculus was accompanied by pyelonephritis or hydronephrosis. Of these, operation was successful in only six. Of eighteen cases of hydronephrosis without stone, only four had a successful result.

In twenty-seven fully recorded cases in which the blood pressure failed to respond to nephrectomy, the operation was clearly indicated on surgical grounds in fifteen. Out of forty-six cases, there were obvious surgical indications for operation in seven. Thirty-three cases showed adequate evidence of unilateral disease, usually a functionless kidney. The main differences between the successes and the failures depended upon: (1) The possibility of reaching a sure diagnosis of unilateral disease; there was a higher incidence of certain diagnosis in the successful than in the unsuccessful cases. (2) A family history of hypertensive disease; such a history was more frequent in the unsuccessful cases. (3) The nature of the disease process; pyelonephritis and congenital abnormalities gave more favorable results than hydronephrosis or calculus.

BELLET.

Reid, G.: Observations on the Part Played by the Vasoconstrictor Substance of Blood Platelets in the Mechanism of Vascular Spasm. M. J. Australia **11**:39 (Aug. 2), 1947.

This paper is concerned with determining whether vasuclar spasm may be produced by the vasoconstrictor substance of defibrinated blood or serum. Eight cats and four dogs were used. In no case did serum or defibrinated blood, when placed around the femoral or anterior tibial artery over lengths up to four centimeters, reduce the outflow from the hind limb. Likewise, no visible effect on the diameter of the vessel was observed. When serum in quantities of 0.5 to 2.0 ml. was injected intra-arterially into the cut stump of the lateral circumflex artery of nine cats and three dogs, including those which had shown no response to serum applied to the femoral artery, there resulted a sharp fall in the outflow from the hind limb, which, in the absence of a commensurable fall in systemic blood pressure or change in capacity, can be attributed only to vasoconstriction.

Ansethetic agent had no effect on the responses to serum. Again, it was thought that more marked effects might be produced if the circulation to the limb was occluded during and for some time after the intra-arterial injection. Occlusion of the common femoral or iliac artery by means of a clip for periods up to ten minutes after the injection of up to 5.0 ml. of serum had no effect in increasing or prolonging the vasoconstriction which was demonstrable after the circulation had been released, but usually the preliminary vasodilation did not occur. Occlusion of the main vessel did not affect the action of serum placed around the main vessel distal to the occlusion.

It was found that the placing of serum or defibrinated blood around the femoral artery produced no change in the diameter of the vessel whether the animal was given heparin or not. When an artery was divided in an animal which had received heparin, contraction of the vessel wall and hemostasis occurred, while the arterial blood pressure remained high. The results described so far lend no support to the view that the vasoconstrictor substance of serum is responsible for localized arterial spasm.

The main question for discussion is whether spasm, either locally or in the peripheral field of the damaged vessel, may be attributable to a humoral agent derived from blood platelets and present in shed blood. The author's experiments indicate that the humoral agent in shed blood is not responsible for localized arterial spasm. It may be a factor in maintaining constriction in the peripheral field of an artery, which has been damaged, thrombosed, or occluded by emboli, provided that the circulation is inadequate to remove it or that it continues to be liberated. A further possibility is that the effects of spasm in a damaged artery or simple mechanical obstruction of it may be aggravated by a peripheral constriction interfering with a collateral circulation.

The author concludes that vascular spasm may be attributable to either stimulation of nerve fibers in the wall of the vessel, resulting in constriction either directly or by reflex means, or to stimulation of smooth muscle by an adequate mechanical stimulus or by a humoral agent. The vascular constriction which results may be localized to a segment of artery or may involve its peripheral field or collaterals.

BELLET.

Nelson, W., Mayerson, H. S., Clark, J. H., and Lyons, C.: Studies of Blood Volume in Tetralogy of Fallot and in Other Types of Congenital Heart Disease. J. Clin. Investigation **26**:800 (Sept.), 1947.

These authors determined the hematocrit, hemoglobin, total circulating hemoglobin, plasma protein, and total plasma protein, plasma volume, red cell volume, and bood volume in seven cases of the tetralogy of Fallot, in four cases of isolated interventricular septal defect, and in one case each of Eisenmenger complex, isolated pulmonic stenosis, coarctation of the aorta, congenital mitral stenosis, and patent ductus arteriosus.

It was found that the plasma volume in the tetralogy of Fallot, contrary to previous investigations, was not significantly nor consistently reduced but rather was normal or slightly increased; however, the red cell volume and total blood volume were markedly increased. The authors suggest that the factor in the tetralogy mainly responsible for this increased red cell volume is the pulmonary stenosis and not the septal defect, since patients with isolated septal defect and the Eisenmenger complex showed normal or slightly increased hemoglobin, red cell volume, and plasma volume whereas those whith isolated pulmonic stenosis had a high red cell volume and hemoglobin (not nearly as high as in the tetralogy) and slightly increased plasma volume. The pulmonic stenosis in the tetralogy forces about 75 per cent of the blood from the right ventricle into the systemic circulation instead of through the lungs. No explanation was found for the high red cell volume in isolated pulmonic stenosis since, in this anomaly, there is no oxygen unsaturation and, therefore, an absence of stimulus for the increased red cell production. Likewise, the reason for the high cell volume and plasma volume in patent ductus arteriosus and congenital mitral stenosis is not known, since the blood oxygen is not unsaturated in thses states.

The authors showed that the red cell volume and blood volume in tetralogy diminished with bed rest and after the Blalock operation. They believe the determinations made by them are useful in diagnosis of congenital heart disease; in deciding when to operate in tetralogy; and as a measure of the beneficial effects of the surgical procedure.

WAGNER.

Danowski, T. S., Winkler, A. W., and Elkinton, J. R.: Biochemical and Hemodynamic Changes Following the Subcutaneous Injection of Glucose Solution. J. Clin. Investigation **26**:887 (Sept.), 1947.

The authors state, "it is well known that the loss of extracellular electrolyte such as occurs in Addison's disease, etc., may contribute to cardiovascular collapse." If this loss is acutely induced it results in a state of shock. It seemed probable that during absorption of glucose given by hypodermoclysis salt is removed from the circulation into this subcutaneous pool in a manner identical with that observed following the injection of fluid intraperitoneally.

This situation was studied experimentally in two dogs and in four patients. In dogs, it was possible to induce salt depletion and shocklike states, with a diminished plasma volume and extracellular fluid volume and increased hematocrit and plasma protein by giving nonelectrolyte glucose solutions subcutaneously. A similar finding was obtained in one patient. In the three other patients there were similar changes, but of a lesser magnitude so that shock was not observed. These changes were not observed when the nonelectrolyte glucose solution was given intravenously.

The authors believe that the salt depletion by subcutaneous administration of nonelectrolyte glucose solutions may precipitate shock if a large quantity is given over a short period of time and if the previous condition of the patient's hemodynamics is bordering on shock. They suggest treatment of the latter state with electrolytes and blood or blood substitutes before administering nonelectrolyte glucose solutions subcutaneously.

WAGNER.

Lenzi, S.: On the Wolff-Parkinson-White Syndrome. Cuore e circolaz. **31**:141 (Sept. Oct.), 1947.

The author presents six cases of the Wolff-Parkinson-White syndrome and reviews all theories which have been advanced in order to explain this electrocardiographic picture. He attempts

to divide the cases into two groups. In the first group, the author places cases with organic lesions of the heart; in the second, those with a normal heart. While the syndrome in the latter group of patients could be explained by the theory of pre-excitation, the occurrence of the syndrome in the former group of patients might be explained in various ways, including myocardial lesions, myocardial edema, and altered excitability of the two branches of the bundle of His.

LUISADA.

Pincelli, C.: On the Behavior of Serum Cholinesterase in Cardiac Patients Treated With Digitalis. Cuore e circolaz. **31**:155 (Sept.-Oct.), 1947.

This study was prompted by the theory of Danielopolu that digitalis acts only as a parasympathomimetic drug and that its action is based on inactivation of serum cholinesterase. The author determined the serum cholinesterase in twenty-five cardiac patients in congestive failure, before and after digitalis. These patients presented low values of the cholinesterase before treatment and a sharp rise of cholinesterase after digitalis, if the action of this drug was clinically apparent.

Two alternative explanations of this fact are advanced. None of them seems to confirm the parasympathomimetic theory of Danielopolu.

LUISADA.

Engel, G. L., and Romano, J.: Studies of Syncope: IV. Biologic Interpretation of Vasodepressor Syncope. Psychosom. Med. **9**:288 (Sept.-Oct.), 1947.

The authors present the concept that vasodepressor syncope results when the primitive reflex preparation for flight or struggle is initiated but then, for some reason, appropriate action becomes impossible or must be inhibited. They describe the physiologic changes occurring during vasodepressor syncope as follows: decreased blood flow to the skin, initial accelerated pulse, increased respiration, sudden slowing of pulse rate, diminution of muscle tone, decrease of peripheral vascular resistance, and fall of blood pressure, which, when it reaches a critically low level, causes the patient to lose consciousness and fall. Vasodepressor syncope seems to occur in settings of real, threatened, or fancied danger when appropriate action is inhibited or impossible. The most common example is the faint following venipuncture. Pain and response to injury may also lead to vasodepressor syncope.

BELLET.

Wendholz, F., and Grayson, C.: Roentgen Demonstration of Calcifications in the Interventricular Septum in Cases of Heart Block. Am. J. Roentgenol. **58**:411 (Oct.), 1947.

The mitral annulus fibrosus is not a complete ring. It encircles the mitral ostium on three sides, being absent at the root of the aorta, and ends on either side in a fibrous nodule, the trigona fibrosa. The ring is completed by a system of fibers from the trigonum fibrosum and is reinforced by bundles from the fila coronaria. This explains why, in a large majority of cases, calcarious deposits in the mitral annulus fibrosus are shaped like the letters *C*, *J*, or *U*. If a completely calcified ring is present, then not only the metral annulus but also the fibrous trigones and the space between them are involved.

Calcium deposits in the valves, annulus fibrosus, and adjacent fibrosus tissue occur in 7.5 to 8.7 per cent of all autopsies. The deposits are usually first seen in the posterior third of the mitral ring with extension toward the right trigonum and the septum. In the latter region there is a division, with one extension going into the trigonum and the other into the posterior or lower portion of the membranous septum. With heavier calcification, there may be a continuation across the space between the trigones into the opposing portions of the trigona and into the adjacent bundles of the aortic ring and fila coronaria. In these cases a complete or crescentic ring is formed around the mitral ostium.

Calcifications in the aortic area begin at the root of the valves. Caudad extensions from the right semilunar valve usually involve the membranaceous septum. Calcifications of the septum are first located in the region of the bifurcation of the conduction bundle and then in the region

of the crus commune. The bundle itself usually is displaced, then stretched, degenerated, and finally calcified.

By means of careful roentgenoscopic examination, the position for best visualization of the involved valves was determined and corresponding roentgenographic exposures were made. Three types of roentgen signs were recognized that were indicative of the presence of calcification in the membranaceous septum:

(1) Caudad extension of calcium shadows from calcified aortic valves or rings. The authors observed two cases which were associated with heart block. No case with such extension was observed in which heart block or prolonged conduction time was not recorded.

(2) Complete circular or crescentic calcification about the mitral ostium. Eight complete ring calcifications were observed in twelve cases of heart block and in two of twenty-one cases without heart block.

(3) Incomplete mitral ring calcifications with nodular thickening of calcareous deposits at the right end of the posterior branch of the calcified mitral ring. This type of calcification was found almost as frequently in those cases without as in those with heart block.

ZION.

Leigh, E., and Hazelton, A. R.: Six Cases of Cardiovascular Disorder With Peripheral Neuritis. Brit. M. J. **2**:573 (Oct. 11), 1947.

Six cases were chosen from among many men suffering from a common group of symptoms in a prisoner-of-war camp in Siam. The typical symptoms were breathlessness on slight exertion, palpitation, and occasional precordial pain. On examination, tachycardia, abnormal increase of pulse rate on rising from recumbent to upright position, tumultuous heart action, some impurity of the first sound at the mitral area, a pistol shot sound over the femoral artery, and carotid sinus irritability were present. The clinical picture resembled that of the effort syndrome. No cardiac enlargement, edema, or anemia was detected. Reduced sensibility of peripheral distribution to pinprick and deep pressure, sluggish reflexes, and a slight Romberg sign constituted the common neurological findings. Following therapy, abnormalities in physical signs in the heart showed improvement in four out of the five cases in which such signs were present. Carotid sinus irritability disappeared in two out of three cases. The improvement in symptoms began after the third injection of thiamin chloride.

BELLET.

Doniach, I.: Uremic Edema of the Lungs. Am. J. Roentgenol. **58**:620 (Nov.), 1947.

A proportion of uremic hypertensive patients with lift ventricular failure develop a subacute pulmonary edema which may be transitory. The roentgen findings consist of a fine or coarse mottling, spreading out from both hilar regions and leaving a clear zone at the apices, periphery, and bases. This distribution, rather than the nature of the mottling, appears to be typical of subacute pulmonary edema associated with uremia and hypertensive heart failure. This intensive roentgen change is usually out of proportion to the local clinical signs and symptoms, which may be minimal apart from the dyspnea. There is no obvious correlation of the onset of edema with any one of the uremic biochemical findings such as hypoproteinemia or acidosis.

In fatal cases, the most significant change seen in the lungs is a "solid edema" due to a fibrinous or an albuminous intra-alveolar exudate. This exudate is believed to result from a combination of a rise in pulmonary capillary pressure secondary to left ventricular failure and an alteration of capillary permeability resulting from uremia.

In nonfatal cases, the lung changes appear with the onset of failure and resolve with the relief of failure. The blood urea level remained constant in at least one of the cases cited by the author. In a series of fifty uremic patients selected at random and free from signs of heart failure, no roentgen signs of pulmonary edema were encountered.

The roentgen findings, though characteristic of uremic hypertensive heart failure, are not pathognomonic of this condition since these findings may be seen in other conditions of heart failure associated with capillary damage such as rheumatic fever or uncomplicated acute left ventricular failure.

ZION.

Maguire, C. H., and Griswold, R. A.: Further Observations on Penetrating Wounds of the Heart and Pericardium. Am. J. Surg. 74:721 (Nov.), 1947.

The authors report their experience with thirty-three cases of penetrating wounds of the heart and great vessels within the pericardium. Twenty-three of the patients lived long enough to reach the operating room. Two patients died postoperatively, one of cerebral embolism from mural thrombi on the third day and the other on the second postoperative day from secondary hemorrhage from the cardiac wounds. The cause of death was exsanguination in the ten patients who died on admission to the accident room or before exploration was possible.

Several points were stressed by the authors. A well-trained resident staff who are sufficiently familiar with wounds of the heart to make an accurate diagnosis and effect prompt operative treatment is essential. The operation should be carried out without delay, but careful preparation of the patient's skin and adequate scrubbing by the surgical team must not be neglected. Positive pressure oxygen with nitrous oxide is the anesthetic of choice. The most satisfactory incision is a transverse one near the site of the wound with resection of one costal cartilage and, if necessary for exposure, division of the adjacent costal cartilages. The wound in the heart or great vessel is sutured and if possible the sutures are not placed through to the endocardium. The pericardium is not closed but left open so fluid can flow into the left pleural space. No external drainage is employed. Postoperatively, one or two aspirations of the left pleural space are usually necessary.

Diagnostically, the triad described by Beck is helpful. A falling arterial blood pressure associated with a rising venous pressure in the presence of a quiet heart constitutes the triad. The authors point out that the general condition of these patients and the shock are out of proportion to the extent of the obvious wound. The wounds have usually been caused by three types of weapons: a knife, ice pick, or pistol.

LORD.

Stutzman, J. W., Murphy, Q., Allen, C. R., and Meek, W. J.: Further Studies on the Production of Cyclopropane-Epinephrine Tachycardia. Anesthesiology 8:579 (Nov.), 1947.

This study was undertaken to determine the site of action of cyclopropane in sensitizing the heart to injected epinephrine. The test dose of epinephrine which was injected intravenously varied from 0.005 to 0.01 mg. per kilogram but remained constant for any one experiment. In each case the dose was sufficient to produce ventricular tachycardia, lasting from fifteen to eighty-five seconds, in the intact anesthetized dog. First, preparations were made in which the body but not the brain was exposed to cyclopropane. Second, three crossed circulation experiments were carried out so that cyclopropane might be restricted either to the brain or to the remainder of the body.

In the first six animals both cyclopropane and epinephrine were restricted to the body circulation by clamping the cerebral blood supply. Each of these animals developed ventricular tachycardia and in three animals this immediately passed into ventricular fibrillation. Cyclopropane and epinephrine were likewise restricted to the body circulation of the recipient in crossed circulation experiments on two dogs. Again ventricular tachycardia was at once produced. Cyclopropane was allowed to reach the entire animal while epinephrine was restricted to the body circulation in three dogs. This also resulted in ventricular tachycardia.

In three of the animals which had previously had temporary occlusion of the cerebral circulation and in the three dogs in which crossed circulation experiments were performed, an anemic decerebration was induced by occluding the cerebral blood flow for thirty minutes. Cyclopropane and epinephrine were then restricted to the body circulation. In contrast to previous experiments, ventricular tachycardia was no longer produced. It was also found that there was no ventricular tachycardia with epinephrine injection when cyclopropane was allowed to circulate only in the cerebral circulation of the recipient.

From the results of these experiments it is evident that for the production of cyclopropane-epinephrine tachycardia cyclopropane and epinephrine do not have to reach the cerebral circulation, but certain brain centers must be intact and functioning. Furthermore, the addition of

cyclopropane to the cerebral circulation does not alter the duration of the cardiac irregularity. It appears, therefore, that the heart is reflexly sensitized by cyclopropane.

In an attempt to locate the afferent pathway of such a reflex the spinal cord was cut below the main cardiac sympathetic outflow. These experiments suggest that afferent impulses entering the cord below T 6 are involved in reflex sensitization of the heart. Bilateral supradiaphragmatic splanchnicotomy and sympathetic chain resection from T 9 to L 1 were done in fifteen dogs. This procedure afforded complete protection from ventricular tachycardia in thirteen of the animals. In the remaining two, a cord section of T 11 resulted in protection. It was found that bilateral adrenalectomy alone does not interfere with the production of ventricular tachycardia.

Additional experiments indicate that cyclopropane stimulated receptors located in the mesentery. A ventricular tachycardia could be prevented by removal of the mesentery to the ileum and jejunum.

The authors conclude that cyclopropane reflexly sensitizes the heart of the dog to injected epinephrine. The receptors are distributed for the most part throughout the peripheral 3 cm. of mesentery. Impulses travel by visceral afferent fibers through the celiac and superior mesenteric plexuses, splanchnics, and spinal cord to a brain center above the pons. Efferent impulses then pass to the heart by way of the cardiac sympathetics and increase the irritability of the heart.

BELLET.

Freeman, A. M.: Acute Postpartal Heart Failure, A Report of Four Cases With an Inquiry Into Pathogenesis. J. M. A. Alabama **17**:163 (Nov.), 1947.

The author presents four cases of acute heart failure which appeared during the puerperium and which responded promptly and apparently completely to measures commonly employed in heart failure.

The heart failure occurred at term in two cases and three weeks and two months post partum, respectively, in two other cases. The precipitating factors were sudden increase in work after bed rest in two cases, and administration of intravenous fluids in the two other patients.

The author reviews the literature on this subject and emphasizes the increase in the work of the heart which occurs in pregnancy as an important factor in the precipitation of heart failure. Additional factors to this heart failure have been the occurrence of toxemia of pregnancy and the presence of hypertension and anemia.

BELLET.

Levy, T.: Case Report of Mechanical Right Heart Failure From Extension of an Undiagnosed Bronchiogenic Carcinoma. South. M. J. **40**:892 (Nov.), 1947.

The patient, a 34-year-old man, had been short of breath for several months, especially on exertion. His acute illness began with a sore throat which lasted a week or ten days and was accompanied by an acute cold and cough. The cough continued and was accompanied by soreness in the left chest. Within the next few weeks a friction rub was heard in the right third intercostal space, anteriorly and laterally. The patient then developed a slight fever and was given 30,000 units of penicillin every three hours for ten days. Following this, he became afebrile. He developed rough systolic murmur which was loudest in the left interscapular region. The electrocardiogram revealed right axis deviation. He began to show signs of a severe grade of heart failure and reacted poorly to treatment. Death occurred about two months after the onset of acute symptoms.

The pertinent necropsy finding was the presence of a large oat-cell carcinoma, arising at the bifurcation of the trachea, extending through the pericardium, compressing the pulmonary artery, occluding the right branch by invasion, and resulting in right-sided heart failure.

BELLET.

Loewe, L., Hirsch, E., and Grayzel, D. M.: The Action of Heparin on Experimental Venous Thrombosis. Surgery **22**:746 (Nov.), 1947.

The authors produced thrombosis in the jugular veins of rabbits. The veins were dissected free from the surrounding tissues and the proximal portion securely tied with a silk ligature. A

narrow ribbon retractor was placed under the vein distal to the ligature and the vein tapped briskly fifteen to thirty times with the handle of a scissors. Bleeding occurred from the veins but was controlled by gauze pressure. A clot which was visible and palpable usually formed. Heparin was instituted from one to fourteen days after trauma in an attempt to evaluate its effect on preformed thrombi. Heparinization was accomplished by administering heparin in Pitkin's menstruum. Heparin, 40 to 100 mg., was given every two to three days and no hemorrhages were observed in any of the animals. At regular intervals the jugular veins were exposed, removed, and examined microscopically in each group of animals.

Several facts were demonstrated: patency of a vein can be re-established, following clot formation, in a large number of experiments by means of adequate heparinization beginning as long as six days after the incident of trauma; the extent and speed of recanalization is enhanced by the use of heparin; in the presence of occluded veins the opening of adjacent collateral venous channels is extensive in the presence of heparin therapy.

Theoretical considerations are discussed in an attempt to explain the ways in which heparin is able to bring about the dissolution of relatively recent clots and to aid and abet recanalization and the formation of collateral circulation in older organized thrombi.

LORD.

Welch, K. J.: Failure of the Peritoneal-Button Operation for Ascites, Report of Two Cases. New England J. Med. **237**:735 (Nov. 13), 1947.

The author reports his experience with two patients who were provided with peritoneal buttons and were ultimately subjected to post-mortem examination.

Case 1 is that of a 57-year-old man with a diagnosis of portal cirrhosis. The patient was admitted to the hospital for operation after a period of recurrent ascites lasting three and one-half months. Fifteen days after a glass peritoneal button had been inserted, he was discharged from the hospital with no evidence of reaccumulation of peritoneal fluid. However, less than one month after operation, fluid had reaccumulated so that he again required paracentesis. The patient died three months later after a massive gastrointestinal hemorrhage from the rupture of an esophageal varix. Post-mortem examination revealed a collapsed subcutaneous cystic space measuring 10 by 7 by 4 cm. which communicated with the peritoneal cavity.

Case 2 is that of a 46-year-old man, with a history of having consumed over a pint of whisky a day for many years. He was admitted to the hospital with a diagnosis of portal cirrhosis following four months of recurrent ascites that required frequent abdominal paracentesis. A peritoneal button was inserted, but in spite of this fluid continued to accumulate, and repeated paracenteses were again necessary. Five weeks later, at the time of death, a massive collection of ascitic fluid had again developed. Post-mortem examination revealed that the peritoneal layer blended evenly with the wall of the canal provided by the button and was continuous with the lining of the subcutaneous space.

In both cases, subcutaneous pockets, which had dense, hyalinized, connective tissue walls, communicated with the peritoneal cavity.

BELLET.

Duguet, J., Dumont, P., and Bailliart, J.: The Effects of Anoxia on Retinal Vessels and Retinal Arterial Pressure. J. Aviation Med. **18**:516 (Dec.), 1947.

The purpose of this investigation was to study the effects of high altitude on the retinal vessels. The retinal circulation is relatively independent of the general circulation and has often been compared with the circulation of the brain. Changes in the retinal vessels were studied by photographing the retina, first, at ground level and then at various altitudes. The authors found that dilatation of the retinal vessels becomes noticeable and can be measured on photographs when an altitude of 4,000 meters is reached; dilatation increases with altitude and reaches its maximum at 6,000 meters, but does not increase after the subject has been at that level for fifteen minutes.

The authors also studied arterial pressure changes by Bailliart's ophthalmodynamometer. Their research was limited to ascertaining the changes of the retinal diastolic blood pressure in

anoxia, since its measurement is always more precise than measurement of the systolic pressure. Measurements were made on seven subjects, first, at sea level, then when conditions in the decompression chamber simulated an altitude of 6,000 meters, and, finally, after a period of at least fifteen minutes at this simulated level. Studies were repeated at the same simulated altitude while the subject breathed oxygen and again when he returned to the conditions at sea level. Ocular tension and systemic arterial pressure were also measured under similar conditions.

The findings show that, under the influence of altitude, variations of diastolic blood pressure in retinal arteries can be classified into two main types which are quite similar to the response of the systemic blood pressure to high altitude. In the first type the reaction to anoxia consists of a rise of retinal arterial pressure which is generally concomitant with a rise of systemic blood pressure and shows a tendency to return to normal values when the duration of the stay at this altitude is prolonged. In the second type of reaction, on the contrary, there is a fall of retinal arterial pressure which is accompanied by a fall of systemic pressure, systolic and diastolic, and which increases with the duration of the stay at this altitude. Patients who react in the latter way seem to have less resistance to anoxia than those who show the first type of reaction and may have a greater tendency to collapse. The authors are inclined to think that anoxic changes in retinal blood pressure are mainly the consequence of the manner in which the intracranial pressure reacts to the same abnormal conditions.

BELLET.

McMillan, R. L., and Welfare, C. R.: Chronic Auricular Fibrillation. J. A. M. A. 135:1132 (Dec. 27), 1947.

The authors studied fifty unselected cases of auricular fibrillation. Of the fifty patients, in forty-four (88 per cent) normal rhythm was restored and persisted from one month to two years in twenty-five (50 per cent). Forty-six per cent of the patients had rheumatic heart disease; 32 per cent had arteriosclerotic heart disease, and the remaining 22 per cent had thyrotoxic heart disease, hypertensive cardiovascular disease, or combinations of these conditions.

All patients were admitted to the hospital and observed for several days before quinidine treatment was begun. Repeated electrocardiograms were made before, during, and after quinidine therapy. Complete digitalization was effected in each case before quinidine therapy was instituted. An attempt was made to observe changes in cardiac efficiency, before and after reversion to normal rhythm, by daily measurements of vital capacity and by determinations of the venous pressure and circulation time. Roentgen studies before and after the restoration of normal rhythm failed to show consistent changes in the size of the auricles. In eighteen patients of the series, determinations of the vital capacity revealed an average increase of 270 c.c. with return to normal rhythm. In thirteen patients whose venous pressure was estimated, an average decrease of 20 mm. of saline solution was found after the return to normal rhythm. In fourteen patients, the circulation time decreased an average of 6.7 seconds.

In this series, failure to revert to normal rhythm bore little relationship to the degree of failure present, the age of the patient, or the duration of the fibrillation. In every case of thyrotoxic heart disease, treatment of the auricular fibrillation was unsuccessful until the underlying hyperthyroidism had been corrected. Five patients (10 per cent) of this series had thyrotoxicosis, either alone or in combination with advanced rheumatic heart disease. Two failures occurred (40 per cent). Three failures occurred in sixteen patients with arteriosclerotic heart disease (failure rate of 18.7 per cent); whereas in twenty-three patients with rheumatic heart disease, treatment was unsuccessful in only one case, a failure rate of 4.3 per cent. Fourteen patients with rheumatic heart disease have maintained a normal sinus rhythm for periods varying from four months to two years. Only 50 per cent of these patients are on maintenance doses of quinidine.

The patients in the 40- to 49-year age group stand out as having the most favorable course; 50 per cent of the twenty patients in this group have had regular rhythm for four months or more. Patients whose auricular fibrillation was abolished on doses of only 0.2 to 0.3 Gm. of quinidine sulfate every four hours are most likely to maintain normal rhythm. However, the necessity for huge doses does not preclude a favorable course. The etiology of the heart disease seems to be

the dominant factor in the success of treatment. Seventy-one and four-tenths per cent of the patients who still maintain a regular rhythm after four or more months had rheumatic heart disease. Eleven of the fifty patients studied have died. Four of these patients had had no quinidine for more than four days at the time of their death.

These authors feel that although the use of quinidine is attended by certain dangers, the incidence of serious cardiovascular accidents in patients treated with quinidine judiciously is little, if any, greater than in similar patients treated without quinidine.

BELLET.

Wilens, S. L.: The Relationship of Chronic Alcoholism to Atherosclerosis. J. A. M. A. 135:1136 (Dec. 27), 1947.

The purpose of this paper is to report the incidence of atherosclerosis in 519 persons 35 years of age or older, who were chronic alcoholics and who have been studied at necropsy. The findings in this group were compared with those in a control group of 600 consecutive necropsies on subjects 35 years of age or older at death, who were total abstainers or moderate consumers of alcohol.

In approximately one-half of the 519 alcoholics, the daily consumption of alcohol was known to have exceeded one pint of whisky, or its equivalent in other forms of alcoholic beverage, for many years. In the alcoholic group as a whole, atherosclerosis was considerably less common and less severe than in the control group of persons who consumed no alcohol or moderate amounts. Lesions that may be attributed to atherosclerosis of the coronary and cerebral arteries were only one-half to one-third as common in the alcoholic addicts as in the control series. However, in excessive alcoholics both severe and moderate degrees of atherosclerosis may develop with some frequency. Three-fourths of both men and women of the control series were 55 years of age or older at death. Only one-half of the alcoholic men and one-fourth of the alcoholic women survived beyond the age of 55 years.

The relatively low incidence of terminal hypertension or lack of evidence of antecedent hypertension as suggested by the low incidence of cardiac hypertrophy in the alcoholic group may have been an important factor. Diabetes was rare in the chronic alcoholics of this series. There were no striking differences in body weight in the two groups, but obese and underweight persons were more numerous in the nonalcoholic series. The 27.9 per cent incidence of cirrhosis in this alcoholic group was considerably higher than has been reported. The incidence of severe, moderate, and mild generalized atherosclerosis was 8.3, 33.1, and 58.8 per cent, respectively, in the alcoholic addicts with cirrhosis, and 14.4, 31.6, and 54.6 per cent, respectively, in the alcoholic addicts without cirrhosis.

Comparison of alcoholic men with hypertension with nonalcoholic men with hypertension revealed a higher incidence of severe atherosclerosis in the nonalcoholic group. Of the nonalchoholic hypertensive men, 24.6 per cent were obese; of the alcoholic hypertensive men, only 19.8 per cent were over weight. In the nonhypertensive groups, 73.5 per cent of the nonalcoholic but only 44.8 per cent of the alcoholic men were underweight.

Differences in incidence of atherosclerosis observed in alcoholic and nonalcoholic groups at necropsy were not considered to be the result of alcoholism, per se, but were considered to be attributable to associated differences in age, blood pressure, and nutrition. The low incidence of myocardial and cerebral lesions resulting from atherosclerosis in persons who were chronic alcoholics was considered to be attributable, to some extent, to factors of age and blood pressure. In the hypertensive group, however, both cerebral and cardiac lesions were somewhat more common in nonalcoholic persons than in persons who were chronic alcoholics.

The author concludes that the substitution of alcohol for a large portion of ordinary foods in the diet does not have an appreciable effect on the development of atherosclerotic lesions. The apparent low incidence of atherosclerosis observed in chronic alcoholism is explained by the relatively young age at death, the low incidence of hypertension, and a lesser tendency for lesions in the heart and brain to develop, particularly in the presence of hypertension. The impli-

cation of this finding is that the materials deposited in atheromatous lesions are not necessarily derived as such from ingested food but that they may be elaborated within the body from other substances.

BELLET.

Gubergrits, A. Y.: Occult Injuries to the Heart. Am. Rev. Soviet Med. **61** (Dec.-Jan.), 1947-1948.

This communication deals with twenty-six patients who managed to survive the lodgment of foreign bodies in the heart. This in the experience of the author is not rare and was observed in 0.5 per cent of all patients with penetrating thoracic wounds who were encountered in the rear evacuation hospitals. It was found that survival after heart injuries was more frequent when the lesion was caused by a splinter from aviation bombs and land mines. Splinters were localized in the large vessels in two cases and in the cardiac musculature in twenty-four cases. The muscle of the left ventricle was involved fifteen times, the wall of the right ventricle seven times, the wall of the right atrium once, and that of the left atrium once. In no case was the foreign body found within the cavities of the heart. In most cases the diagnosis of foreign body in the heart was missed at the medical aid posts. The correct diagnosis was made in evacuation hospitals in twenty of twenty-six cases.

The reason for overlooking foreign bodies in the heart lies in the emphasis on lung rather than on heart injuries. Too little attention, therefore, is paid to changes in density of the heart shadow which are particularly important for the detection of small metal splinters. Among the complaints of the patients, precordial pain ranked first. The pain was stinging, and occasionally oppressive and intermittent, but unlike anginal pain, did not radiate to the periphery. Palpitation was a common complaint and was present in all but five patients.

The diagnostic method of choice for the location of a foreign body in the heart is the x-ray examination. It is essential to ascertain by this method whether the foreign body is situated within the cavity, in the wall of the heart, or whether it lies near the cardiac shadow. Fluoroscopy is the most valuable method in the diagnosis of foreign body injuries of the heart.

The working capacities of these patients may be reduced but little by such an injury; in many instances no symptoms were initially present. In most instances, however, cardiac weakness became evident later.

BELLET.

Adelman, M. H.: Anesthesia in Surgery of the Patent Ductus Arteriosus. Anesthesiology **9**:42 (Jan.), 1948.

The purpose of this paper is to report the author's experiences with the anesthetic problems incident to the surgical ligation of a patent ductus arteriosus in thirty patients. Ten patients had subacute bacterial endarteritis of the ductus. Twenty-nine patients had good cardiac reserve with no evidence of failure. One patient had heart failure with dyspnea and orthopnea of three months' duration. In the majority of cases the lung parenchyma was normal. There was no surgical manipulation or traction of pulmonary structures. The operation concerned itself only with the patent ductus and its associated great vessels. The operative procedure, per se, produced no cardiac disturbances or arrhythmias.

In one case Avertin-cyclopropane was used, in nineteen cases cyclopropane was the sole anesthetic agent, and in the ramaining ten cases, cyclopropane-ether mixtures were used, cyclopropane being the primary anesthetic agent. Cyclopropane offers the advantages of rapid induction and quiet, unstimulated respirations. The author has been adding small amounts of ether (15 to 25 c.c.) to cyclopropane; this has served to combat the tendency toward laryngospasm and cardiac arrhythmias which tend to result from cyclopropane alone. No cases of "cyclopropane shock" were observed. As for the depth of anesthesia, middle second plane was adequate.

The primary anesthetic problem is one common to all chest surgery when an open pneumothorax is produced. This consists in the prevention of "pulmonary decompensation" with excessively active movement of the diaphragm and thoracic cage, shifting of the mediastinum with

each phase of respiration, "pendelluft," hypoxia, and hypercapnia. The surgeon's prime request is for a "quiet chest," an open chest whose movements do not interfere with the surgical procedure. In the majority of cases a quiet chest has been attained by the use of cyclo-ether and irregularly intermittent positive pressure (approximate rate, 8 to 10 per minute) with full insufflation of the lungs about every five or six minutes. Other than cyclopropane arrhythmias and laryngospasm, which necessitated intubation in two cases, there were no anesthetic complications.

BELLET.

Wartman, W. B., and Hellerstein, H. K.: The Incidence of Heart Disease in 2,000 Consecutive Autopsies. Ann. Int. Med. **28**:41 (Jan.), 1948.

This report is a statistical study of the incidence of heart disease in 2,000 consecutive autopsies performed over a five-year period. Sixteen per cent of the 2,000 subjects were under 5 years of age. Nine hundred eighty-four of the patients had a cardiac lesion, although not all of the lesions were sufficiently important to have contributed to death. One hundred forty subjects had rheumatic heart disease of which cases sixteen were complicated by subacute bacterial endocarditis. Two hundred seventy-one persons had hypertensive heart disease of which number the majority also had coronary artery disease. There were 272 cases of coronary artery disease without hypertension. Only seventy-seven patients with hypertension had simple uncomplicated enlargement of the heart.

Forty-nine persons with rheumatic carditis lived to be 45 years old or more. Thirty-four had an active process, of which nine were primary without evidence of previous rheumatic carditis. Twenty-five had acute verrucous endocarditis superimposed on a chronic process. The mitral valve was involved in every instance except in two cases where there was an isolated aortic valvular lesion.

Five-hundred two (51 per cent) of the total of 984 persons with heart disease had coronary artery disease. Of those with coronary artery disease, 160 persons had myocardial infarcts of which 111 were of relatively recent origin. A statistical breakdown of these 160 cases of myocardial infarction revealed the following: The infarcts were single in ninety-four instances and multiple in sixty-six. Regarding localization of the infarcts, the lesion was limited to the left ventricle in 134 cases, to both left and right ventricle in eighteen cases, to the right atrium alone in four cases, and to the right ventricle alone in four cases. In five cases, isolated infarction of the interventricular septum was present. The infarct involved the anterior and posterior portion of the left ventricle in 72 per cent and 28 per cent, respectively. Of the total number with anterior wall infarction, in 54 per cent of the lesion extended to involve the anterior half of the interventricular septum. Of the total number with posterior wall infarction, the lesion extended into the posterior half of the interventricular septum in 25 per cent. Lateral wall infarction, whether alone or in combination with infarcts in other locations, was relatively infrequent. Infarction of the myocardium was associated with actual occlusion of the nutrient coronary artery in 82.5 per cent. In 13.7 per cent there was disease of the coronary artery without occlusion. In 3.8 per cent myocardial infarction occurred without coronary artery obstruction or disease. In 16 per cent a coronary artery was found to be occluded without any infarction occurring distal to the point of obstruction. Most of the persons in this group had died within three hours of the earliest onset of clinical symptoms. Of the 160 persons with myocardial infarcts, 40 per cent had mural thrombi in direct contact with the infarcted area. Of the 111 with recent myocardial infarcts, acute fibronous pericarditis overlying the myocardial lesion was found in 28 per cent. Fifty-five per cent of the persons with intracardiac thrombi had occlusion of peripheral vessels from either thrombi or emboli. Ventricular aneurysm, as a complication of myocardial infarction, occurred in 22 per cent (thirty-five cases). Mural thrombi commonly occurred within the ventricular aneurysm. Of the thirty-five cases of ventricular aneurysm, twenty-five occurred in the anterior apical portion of the left ventricle, three in the posterolateral, and seven in the posterobasal portion of the left ventricle. Rupture of the ventricular aneurysm occurred in five of the thirty-five cases. There was also rupture of those infarcts unassociated with aneurysm in two instances. In the majority, the rupture occurred between two to seven days after the onset of clinical symptoms indicative of acute coronary artery obstruction.

WENDKOS.

American Heart Association, Inc.

1775 Broadway, New York 19, N. Y.

Telephone Plaza 7-2045

GOVERNING BODIES OF AMERICAN HEART ASSOCIATION, INC.
Elected June, 1948

OFFICERS

PRESIDENT . . . . . Tinsley R. Harrison, M.D., Dallas, Texas
PRESIDENT-ELECT . . . . . H. M. Marvin, M.D., New Haven, Conn.
VICE-PRESIDENT . . . . . George K. Fenn, M.D., Chicago, Ill.
TREASURER . . . . . Grant Keehn, New York, N. Y.
SECRETARY . . . . . John J. Sampson, M.D., San Francisco, Calif.

BOARD OF DIRECTORS

Andrew W. Robertson, *Chairman*

Class of 1949

*Arlie R. Barnes, M.D., Rochester, Minn.
*George E. Burch, M.D., New Orleans, La.
Justin Dart, Los Angeles, Calif.
George K. Fenn, M.D., Chicago, Ill.
Morris Fishbein, M.D., Chicago, Ill.
Norman E. Freeman, M.D., San Francisco, Calif.
*Tinsley R. Harrison, M.D., Dallas, Texas
T. Duckett Jones, M.D., New York, N. Y.
Louis N. Katz, M.D., Chicago, Ill.
Grant Keehn, New York, N. Y.
Robert L. King, M.D., Seattle, Wash.
William B. Kountz, M.D., St. Louis, Mo.
*H. M. Marvin, M.D., New Haven, Conn.
Irvine H. Page, M.D., Cleveland, O.
Thomas I. Parkinson, New York, N. Y.
*David D. Rutstein, M.D., Boston, Mass.
*John J. Sampson, M.D., San Francisco, Calif.
Harry E. Ungerleider, M.D., New York, N. Y.
Carl J. Wiggers, M.D., Cleveland, O.
*Irving S. Wright, M.D., New York, N. Y.

Class of 1950

Edgar V. Allen, M.D., Rochester, Minn.
E. Cowles Andrus, M.D., Baltimore, Md.
William H. Bunn, M.D., Youngstown, O.
*S. De Witt Clough, Chicago, Ill.
Charles P. Cooper, New York, N. Y.
*Alfred C. Howell, Bethel, Conn.
George R. Jones, Chicago, Ill.
Mrs. Wendell Kinney, Los Angeles, Calif.
Robert L. Levy, M.D., New York, N. Y.
Thomas M. McMillan, M.D., Philadelphia, Pa.
*Robert L. Mehornay, Kansas City, Mo.
*Howard B. Sprague, M.D., Boston, Mass.

Class of 1951

Mrs. Arthur Baer, New York, N. Y.
Herrman L. Blumgart, M.D., Boston, Mass.
*John H. Dunkin, Tulsa, Okla.
Maurice Goldblatt, Chicago, Ill.
Samuel Harrell, Indianapolis, Ind.
*Andrew W. Robertson, Pittsburgh, Pa.
*Frederick K. Trask, Jr., New York, N. Y.
Maurice Visscher, Minneapolis, Minn.

*Executive Committee.

ASSEMBLY

Class of 1949

Nelson W. Barker, M.D., Rochester, Minn.
Arlie R. Barnes, M.D., Rochester, Minn.
Alfred Blalock, M.D., Baltimore, Md.
Alva Bradley, Cleveland, O.
Earle Brown, Minneapolis, Minn.
George E. Burch, M.D., New Orleans, La.
Edward W. Cannady, M.D., East St. Louis, Ill.
Warren B. Cooksey, M.D., Detroit, Mich.
Justin Dart, Los Angeles, Calif.
Clarence E. de La Chapelle, M.D., New York, N. Y.
Francis R. Dieuaide, M.D., New York, N. Y.
Harvey M. Ewing, M.D., Montclair, N. J.
Richard J. Finnegan, Chicago, Ill.

Morris Fishbein, M.D., Chicago, Ill.
Norman E. Freeman, M.D., San Francisco, Calif.
A. E. Grauer, Vancouver, Canada
Rudolph F. Haffenreffer, Providence, R. I.
Tinsley R. Harrison, M.D., Dallas, Texas
George R. Herrmann, M.D., Galveston, Texas
T. Duckett Jones, M.D., New York, N. Y.
Albert D. Kaiser, M.D., Rochester, N. Y.
Louis N. Katz, M.D., Chicago, Ill.
Samuel H. Kauffmann, Washington, D. C.
Grant Keehn, New York, N. Y.
John D. Keith, M.D., Toronto, Canada
Robert L. King, M.D., Seattle, Wash.
William B. Kountz, M.D., St. Louis, Mo.
Eugene M. Landis, M.D., Boston, Mass.
Clare Boothe Luce, Ridgefield, Conn.
H. M. Marvin, M. D., New Haven, Conn.
Edwin P. Maynard, Jr., M.D., Brooklyn, N. Y

Alfred J. McCosker, New York, N. Y.
Hugh McCulloch, M.D., St. Louis, Mo.
Richard M. Moss, Belleville, Ill.
E. Sterling Nichol, M.D., Miami, Fla.
Irvine H. Page, M.D., Cleveland, O.
Samuel Proger, M.D., Boston, Mass.
Homer P. Rush, M.D., Portland, Ore.
David D. Rutstein, M.D., Boston, Mass.
John J. Sampson, M.D., San Francisco, Calif.
Francis F. Schwentker, M.D., Baltimore, Md.
Arthur Selzer, M.D., San Francisco, Calif.
Isaac Starr, M.D., Philadelphia, Pa.
Eugene A. Stead, Jr., M.D., Durham, N. C.
William D. Stroud, M.D., Philadelphia, Pa.
Homer F. Swift, M.D., New York, N. Y.
J. Ross Veal, M.D., Washington, D. C.
Louis E. Viko, M.D., Salt Lake City, Utah
Joe E. Werthan, Nashville, Tenn.
Carl J. Wiggers, M.D., Cleveland, O.
J. Edwin Wood, Jr., M.D., Charlottesville, Va.

Class of 1950

Edgar V. Allen, M.D., Rochester, Minn.
James Anderson, Philadelphia, Pa.
E. Cowles Andrus, M.D., Baltimore, Md.
Graham Asher, M.D., Kansas City, Mo.
Emmet B. Bay, M.D., Chicago, Ill.
William H. Bunn, M.D., Youngstown, O.
Francis L. Chamberlain, M.D., San Francisco, Calif.
Paul F. Clark, Boston, Mass.
S. De Witt Clough, Chicago, Ill.
Charles P. Cooper, New York, N. Y.
James A. Cunningham, Chicago, Ill.
George K. Fenn, M.D., Chicago, Ill.
Samuel Goldwyn, Los Angeles, Calif.
John Hepburn, M.D., Toronto, Canada
J. G. Fred Hiss, M.D., Syracuse, N. Y.
Alfred C. Howell, Bethel, Conn.
Coleman Jennings, Washington, D. C.
Mrs. Wendell Kinney, Los Angeles, Calif.
Chester M. Kurtz, M.D., Madison, Wis.
Bernard W. Leonard, M.D., Washington, D. C.

Robert L. Levy, M.D., New York, N. Y.
Samuel J. McClendon, M.D., San Diego, Calif.
Johnson McGuire, M.D., Cincinnati, O.
Thomas M. McMillan, M.D., Philadelphia, Pa.
Robert L. Mehornay, Kansas City, Mo.
Robert M. Moore, M.D., Indianapolis, Ind.
Myron Prinzmetal, M.D., Los Angeles, Calif.
Dickinson W. Richards, Jr., M.D., New York, N. Y.
Harold N. Segall, M.D., Montreal, Canada
M. J. Shapiro, M.D., Minneapolis, Minn.
Howard B. Sprague, M.D., Boston, Mass.
Ernest L. Stebbins, M.D., Baltimore, Md.
Alexander Terrell, M.D., Dallas, Texas
Maurice Visscher, M.D., Minneapolis, Minn.
William Paul Thompson, M.D., Los Angeles, Calif.
Carl Whitmore, New York, N. Y.
Irving S. Wright, M.D., New York, N. Y.
J. D. Zellerbach, San Francisco, Calif.

Class of 1951

Oliver Aas, Minneapolis, Minn.
Mrs. Arthur Baer, New York, N. Y.
Herrman L. Blumgart, M.D., Boston, Mass.
Lewis T. Bullock, M.D., Los Angeles, Calif.
Harry C. Carr, Philadelphia, Pa.
Bradley Dewey, Cambridge, Mass.
Thomas E. Dewey, Albany, N. Y.
John H. Dunkin, Tulsa, Okla.
Lawrence B. Ellis, M.D., Boston, Mass.
Emerson Foote, New York, N. Y.
Maurice Goldblatt, Chicago, Ill.
James A. Greene, M.D., Houston, Texas
Robert Z. Greene, New York, N. Y.
Samuel Harrell, Indianapolis, Ind.
Mark H. Harrington, Denver, Colo.
George R. Jones, Chicago, Ill.
Mrs. Edwin H. Koehler, New York, N. Y.
Edgar Kobak, New York, N. Y.
Harold C. Lueth, M.D., Omaha, Neb.
Louis E. Martin, M.D., Los Angeles, Calif.

Frank L. Mechem, Seattle, Wash.
Thomas I. Parkinson, New York, N. Y.
Russell C. Pigford, M.D., Tulsa, Okla.
Ann Purdy, M.D., San Francisco, Calif.
Andrew W. Robertson, Pittsburgh, Pa.
Harold H. Rosenblum, M.D., San Francisco, Calif.
Roy W. Scott, M.D., Cleveland, Ohio
F. Janney Smith, M.D., Detroit, Mich.
Harold E. Stassen, St. Paul, Minn.
Erwin C. Stupp, St. Louis, Mo.
Robert A. Taft, Cincinnati, O.
Frederick K. Trask, Jr., New York, N. Y.
Harry E. Ungerleider, M.D. New York,, N. Y.
Howard F. West, M.D., Los Angeles, Calif.
Paul D. White, M.D., Boston, Mass.
Russell White, Indianapolis, Ind.
Mark Woods, New York, N. Y.

JOURNAL MEMBERSHIP RATE INCREASED

Effective July 1, the annual JOURNAL membership rate is increased from $10 to $12 per year. Six-month JOURNAL memberships are advanced from $6 to $8. Those already holding annual JOURNAL memberships for 1948 will not be affected by the increase until Jan. 1, 1949.

POSTGRADUATE COURSE IN ELECTROCARDIOGRAPHY

The Michael Reese Hospital Postgraduate School in Chicago announces that its Intensive Postgraduate Course for Graduate Physicians in Electrocardiography will be held August 16 through August 28. Presented by Dr. Louis N. Katz, the course will be open to beginning and advanced students and will include group and individual instruction. The tuition fee is $150 and the size of the class is limited. Interested physicians should address Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, 29th St. and Ellis Avenue, Chicago 16, Ill.